






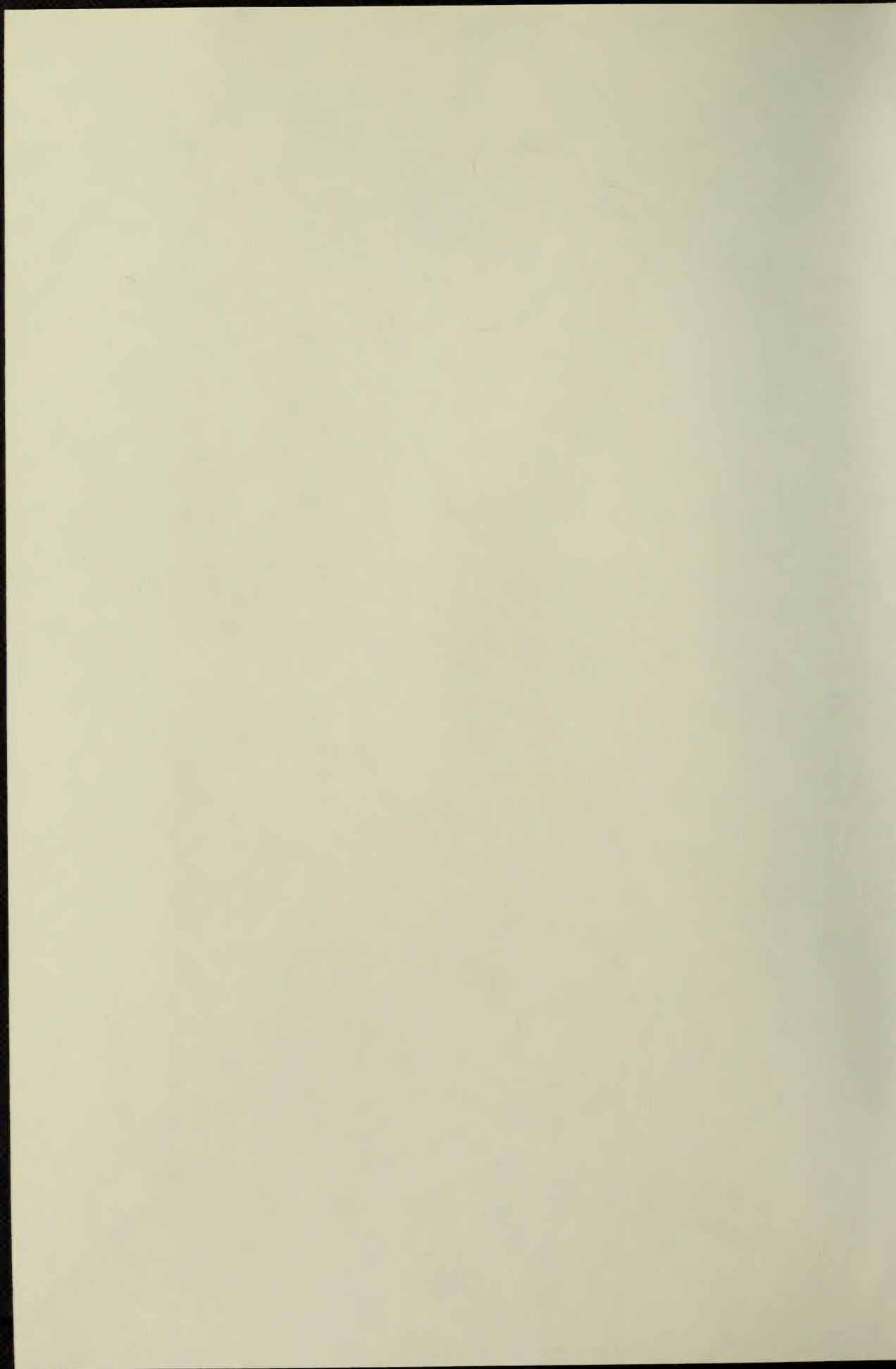
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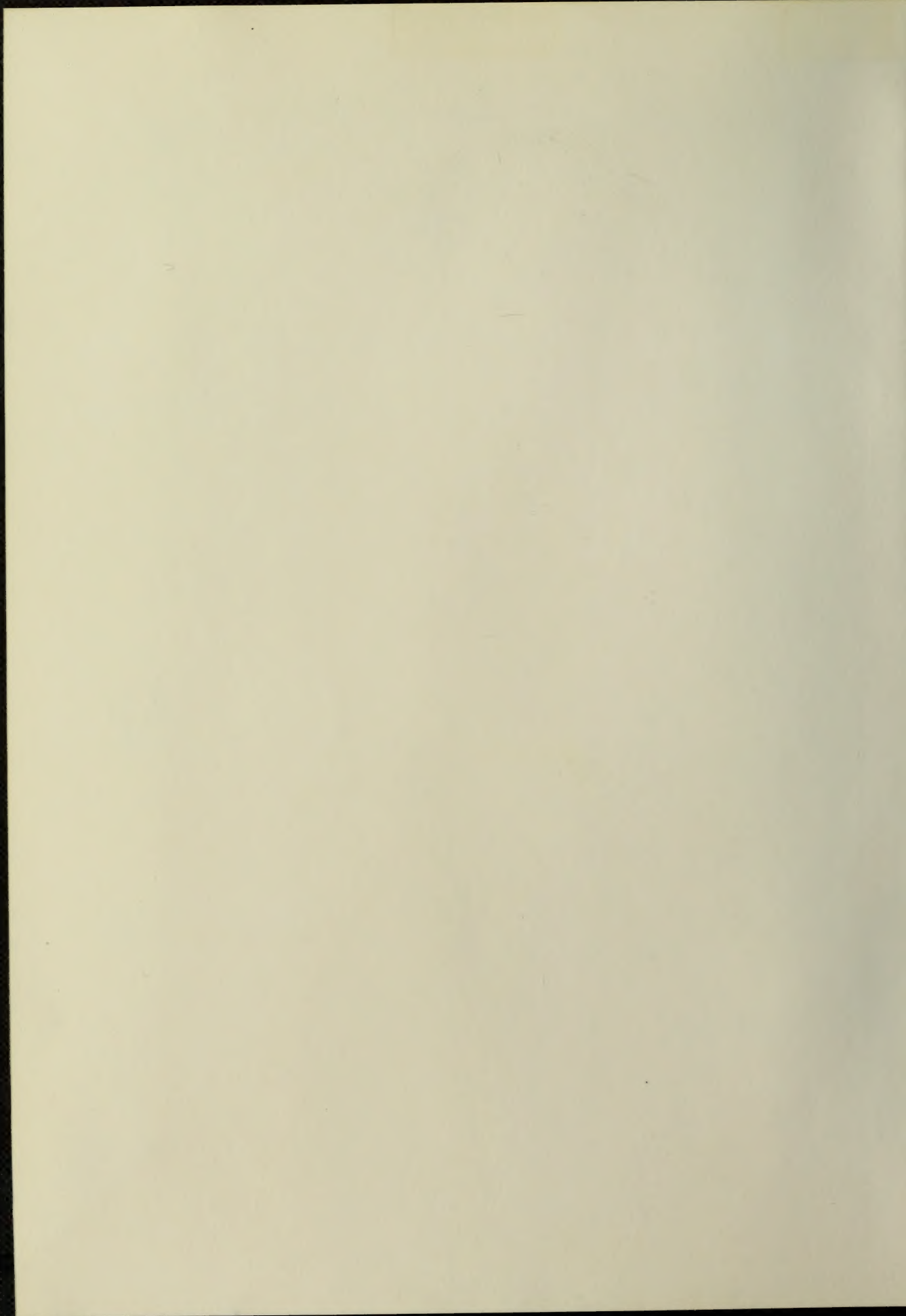




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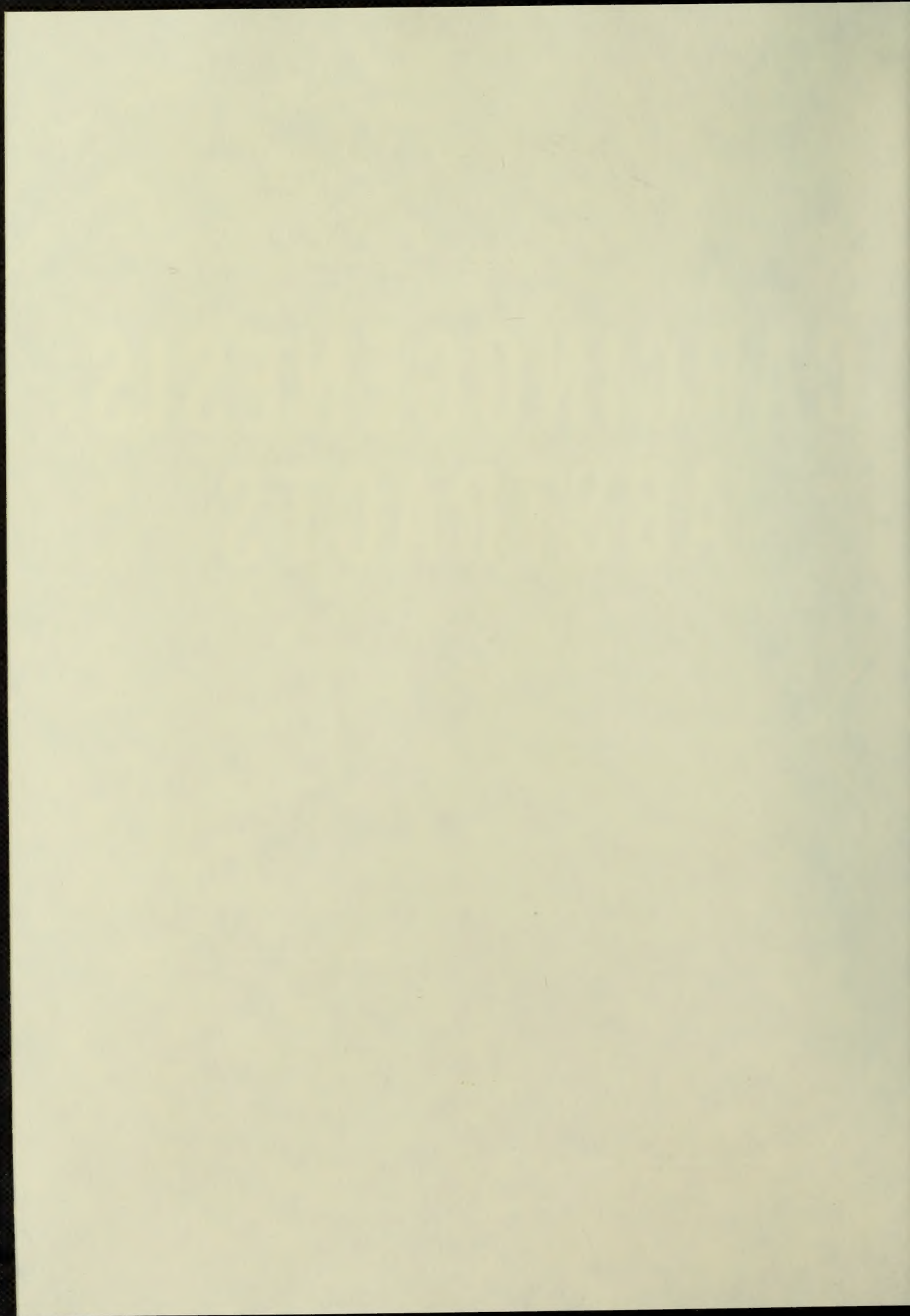
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VOLUME 16  
ISSUE 1



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# CARCINOGENESIS ABSTRACTS

*A monthly publication sponsored by the*  
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## **EDITOR**

**GEORGE P. STUDZINSKI, M.D., Ph.D.**  
COLLEGE OF MEDICINE AND DENTISTRY  
OF NEW JERSEY, NEWARK

## **ASSOCIATE EDITOR**

**JUSSI J. SAUKKONEN, M.D.**  
JEFFERSON MEDICAL COLLEGE  
PHILADELPHIA

## **NCI STAFF CONSULTANTS**

**ELIZABETH WEISBURGER, Ph.D.**  
**JOAN W. CHASE, M.S.**

*Literature Selected, Abstracted, and Indexed*  
*by*

*Information Services Department, Science Information Services Organization*

**BRUCE H. KLEINSTEIN, Ph.D., J.D., Assistant Director, Biomedical Projects**

**RUTHANN E. AUCHINLECK, Managing Editor**

**The Franklin Research Center**  
**The Benjamin Franklin Parkway, Philadelphia, Pennsylvania 19103**

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A monthly publication prepared by the  
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ASSOCIATE EDITOR  
JAMES I. SAUBERMAN, M.D.  
BETHLEHEM MEDICAL COLLEGE  
BETHLEHEM, PENNSYLVANIA

EDITOR  
GEORGE F. FRIEDBERG, M.D., Ph.D.  
COLLEGE OF MEDICINE AND DENTISTRY  
100 NEW BRUNSWICK AVENUE  
NEW BRUNSWICK, NEW JERSEY

ADVISORY EDITORIAL BOARD  
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### GENERAL INFORMATION

CARCINOGENESIS ABSTRACTS makes available abstracts, annotations or citations of significant carcinogenesis articles collected from the current major biomedical sources of world literature. This service is provided by the National Cancer Institute through a contract with the Franklin Research Center for preparation of the publication, under Contract No. NOI-CP-75885 with the National Cancer Institute, U.S. Department of Health, Education and Welfare. Published and distributed by the Franklin Institute Press<sup>SM</sup>.

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## ABBREVIATIONS

**JOURNAL** names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

**LANGUAGE** of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

**ABBREVIATIONS** used in abstracts:

<b>A</b>	angstrom(s)	<b>mOsm</b>	milliosmolar
<b>ACTH</b>	adrenocorticotrophic hormone	<b>max</b>	maximum
<b>ADP</b>	adenosine diphosphate	<b>mEq</b>	milliequivalent(s)
<b>AMP</b>	adenosine monophosphate	<b>min</b>	minute(s)
<b>ATP</b>	adenosine triphosphate	<b>ml</b>	milliliter(s)
<b>approx</b>	approximately	<b>μl</b>	microliter(s)
<b>av</b>	average	<b>mm</b>	millimeter(s)
<b>BCG</b>	bacillus Calmette-Guerin	<b>mo</b>	month(s)
<b>bid</b>	twice daily	<b>mol wt</b>	molecular weight
<b>C</b>	degree(s) centigrade	<b>N</b>	normal concentration
<b>cal</b>	calorie(s)	<b>NAD</b>	nicotinamide adenine dinucleotide
<b>kcal</b>	kilocalorie(s)	<b>NADH</b>	reduced nicotinamide adenine dinucleotide
<b>cc</b>	cubic centimeter(s)	<b>NADP</b>	nicotinamide adenine dinucleotidephosphate
<b>Ci</b>	curie(s)	<b>NADPH</b>	reduced nicotinamide adenine dinucleotidephosphate
<b>mCi</b>	millicurie(s)	<b>NCI</b>	National Cancer Institute
<b>μCi</b>	microcurie(s)	<b>NIH</b>	National Institutes of Health
<b>cm</b>	centimeter(s)	<b>PAS</b>	periodic acid-Schiff
<b>CNS</b>	central nervous system	<b>po</b>	orally
<b>cpm</b>	counts per minute	<b>ppb</b>	parts per billion
<b>DNA</b>	deoxyribonucleic acid	<b>ppm</b>	parts per million
<b>ED<sub>50</sub></b>	median effective dose	<b>qid</b>	four times daily
<b>EDTA</b>	ethylenediamine tetraacetic acid	<b>qod</b>	every other day
<b>g</b>	gram(s)	<b>QO<sub>2</sub></b>	oxygen quotient
<b>kg</b>	kilogram(s)	<b>R</b>	roentgen
<b>mg</b>	milligram(s)	<b>RBC</b>	red blood cells (erythrocytes)
<b>μg</b>	microgram(s)	<b>RNA</b>	ribonucleic acid
<b>Hb</b>	hemoglobin	<b>rpm</b>	revolutions per minute
<b>hr</b>	hour(s)	<b>sc</b>	subcutaneous
<b>ia</b>	intra-arterial	<b>sec</b>	second(s)
<b>id</b>	intra-dermal	<b>SGOT</b>	serum glutamic-oxaloacetic transaminase
<b>IgA</b>	Immunoglobulin A	<b>SGPT</b>	serum glutamic-pyruvic transaminase
<b>IgB</b>	Immunoglobulin B	<b>soln</b>	solution
<b>IgG</b>	Immunoglobulin G	<b>TCD</b>	tissue culture dose
<b>IgM</b>	Immunoglobulin M	<b>TCD<sub>50</sub></b>	median tissue culture dose
<b>ILS</b>	increased life span	<b>tid</b>	three times daily
<b>im</b>	intramuscular	<b>UV</b>	ultraviolet
<b>ip</b>	intraperitoneal	<b>WBC</b>	white blood cells (leukocytes)
<b>IU</b>	International Unit(s)	<b>wk</b>	week(s)
<b>iv</b>	intravenous	<b>wt</b>	weight
<b>Km</b>	Michaelis constant	<b>X</b>	times
<b>LD</b>	lethal dose	<b>yr</b>	year(s)
<b>LD<sub>50</sub></b>	median lethal dose		
<b>M</b>	molar		
<b>μM</b>	micromolar		



## REVIEW

- 78-0001 Mode of Action and Human Health Aspects of Aflatoxin Carcinogenesis.** (Eng) Butler, W. H. (Dept. Histopathology, St. George's Hosp. Medical Sch., Blackshaw Road, London, SW17 0QT, England); Neal, G. E. *Pure Appl Chem* 49(11): 1747-1751; 1977.

The experimental studies of the mode of action of aflatoxins (AF's) are reviewed. In the rat, AF levels as low as 0.015 ppm continuously or a higher short-term dosage is sufficient to induce a high incidence of hepatocarcinoma. Studies of the action of AF's on rat liver indicate that the pattern of events is similar to that of other hepatocarcinogens and that an irreversible change is induced at an early stage. In all studies of experimental hepatocarcinogenesis using AF as the inducing agent, the neoplasm usually arises in the liver in the absence of cirrhosis. In Europe and North America, most hepatocarcinomas arise in cirrhotic patients. In areas where hepatocarcinoma is relatively common, however, many arise in livers showing no cirrhosis. The recognition of AF's as hepatocarcinogens led to the development of the mycotoxin hypothesis for the etiology of hepatocarcinoma in man. Surveys from Kenya, Thailand, Swaziland, and Mozambique demonstrate a good correlation between ingestion of AF and incidence of hepatocarcinoma. Animals on low-lipotrope diets have an increased susceptibility to AF hepatocarcinogenesis, but vitamin A-deficient animals have an increased incidence of AF-induced colonic carcinoma. This suggests that future studies of aflatoxin carcinogenicity should include other neoplastic diseases as well as hepatocarcinogenesis. (23 refs.)

- 78-0002 Metabolism of Aflatoxin and Other Mycotoxins in Relation to Their Toxicity and the Accumulation of Residues in Animal Tissues.** (Eng) Patterson, D. S. (Central Veterinary Lab., Weybridge, Surrey, England KT15 3NB). *Pure Appl Chem* 49(11): 1723-1731; 1977.

The metabolism of the aflatoxins, sterigmatocystin, ochratoxins A and B, and the *Fusarium* toxins is considered with regard to their detoxification, metabolic activation and mode of action, and potential for accumulating as toxic residues in animal tissues. Aflatoxin is metabolized more slowly by some animals and it can constitute a residue problem, particularly in the tissues of farm animals. A considerable public health problem exists in the excretion of aflatoxin M<sub>1</sub> in the milk of dairy cows consuming feed contaminated with aflatoxin. Two hypotheses have been proposed for the metabolic activation of aflatoxin B<sub>1</sub>: (1) it is activated by a metabolic conversion to hemiacetal, which binds to various key enzymes and metabolically important liver cell structures; and (2) it is activated to the hypothetical 2,3-oxide that, because it is muta-

genic, is presumed to be the proximal carcinogen. Pigs exposed to ochratoxin A in their diet accumulate the compound in kidney, liver, and muscle (in decreasing order). Sterigmatocystin, trichothecenes, and zearalenone all pose potential residue problems when domestic animals have been exposed to contaminated feeds. Mycotoxin metabolism may also take place in the skin and gastrointestinal tract, sites that should be investigated further. (33 refs.)

- 78-0003 Some New Mycotoxins.** (Eng) Steyn, P. S. (Natl. Chemical Res. Lab., Council Scientific and Industrial Res., P. O. Box 395, Pretoria 0001, South Africa). *Pure Appl Chem* 49(11): 1771-1778; 1977.

Biochemical advances in the structural chemistry of several new mycotoxins are reviewed. They include compounds that act on the CNS (those containing one N atom and the cyclic peptides), toxic cytochalasins, bisdihydrobenzofuran metabolites, mycotoxins containing the  $\beta$ -tricarboxyl moiety, and highly oxygenated compounds. The significance of these compounds in naturally occurring intoxications is not known. (58 refs.)

- 78-0004 The Mycotoxins and Human Health Hazards.** (Eng) Linsell, C. A. (International Agency Res. Cancer, 150 Cours Albert Thoams, 69008 Lyon, France). *Pure Appl Chem* 49(11): 1765-1769; 1977.

Aflatoxins are potent hepatocarcinogens, and they can induce liver tumors in many experimental animals, including monkeys. Their prevalence in foods in areas with high rates of liver cancer suggests that the association in man is more than casual. The role of mycotoxins in human disease is briefly reviewed, and individual cases of mycotoxicosis and epidemic occurrences are assessed. (31 refs.)

- 78-0005 Mycotoxins and Other Naturally Occurring Carcinogens.** (Eng) Wogan, G. N. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol 3, 388 pp., 263-290; 1977.

Information on carcinogens of natural origin, is reviewed. Aflatoxins, which are produced by *Aspergillus flavus*, have carcinogenic activity in many species of animals, including



rodents, nonhuman primates, birds, and fish. The liver is the organ principally affected, although a significant incidence of tumors at other sites has been recorded. Current knowledge about aflatoxin metabolism is incomplete, but evidence has been obtained for several metabolic pathways, including hydroxylation, O-demethylation, and epoxidation. Four investigations of aflatoxin intake by populations in Africa and Asia, in which primary liver carcinoma occurs at different incidences, established a positive correlation between intake and liver cancer incidence. These data provide strong circumstantial evidence of a causal relationship between aflatoxin ingestion and liver cancer in humans. Other naturally occurring carcinogens include sterigmatocystin and other mycotoxins, pyrrolizidine alkaloids, cycasin and related glycosides, and nitrosamines or nitrosamides formed through the interaction of nitrite and nitrosatable substances. (137 refs.)

- 78-0006 Food Mycotoxins Survey and Monitoring Programs.** (Eng) Campbell, A. D. (Bureau Foods, Food and Drug Admin., Washington, DC 20204). *Pure Appl Chem* 49(11): 1703-1707; 1977.

Examples of effective mycotoxin survey and monitoring programs are reviewed. A well-designed mycotoxin survey program should give the following three pieces of information: (1) whether or not a problem exists; (2) if contamination is found, an indication of its extent; and (3) whether the problem is localized or of a general nature. Several surveys have been conducted on a number of foods in many countries. In the US, surveys have been carried out on Brazil nuts, pistachio nuts, walnuts, almonds, and pecans. Some degree of contamination with aflatoxin was found in each case, and monitoring programs for these foods were started. Points in the harvesting and processing of a crop at which effective monitoring can be performed include the point of purchase, import or export, receipt of raw materials for processing, in-process control, and the finished product. Adequate tools and techniques are available to institute other monitoring programs for other feed and foodstuffs when justified. (21 refs.)

- 78-0007 Mode of Action of Trichothecenes.** (Eng) Ueno, Y. (Dept. Microbial Chemistry, Faculty Pharmaceutical Sciences, Tokyo Univ. Science, Ichigaya, Tokyo 162, Japan). *Pure Appl Chem* 49(11): 1737-1745; 1977.

The toxicological and biological characteristics of 30 trichothecene (TT) mycotoxins, which are produced by a wide range of *Fusarium*, *Myrothecium*, and other fungi, are summarized. The 12,13-epoxytrichothecenes induce nausea, vomiting, skin inflammation, leukopenia, diarrhea, hemorrhage in lung and brain, and destruction of bone marrow, all symptoms of major intoxication in various parts of the world. The accumulated evidence that TT's inhibit peptidyl polymerization and puromycin reactions, cause disaggregation of

polysomes, and bind with active polysomes led to the following conclusion concerning their mechanism of action. TT's interfere with the active center of ribosomal peptidyltransferase and prevent the ribosomal cycle by inhibiting initiation and termination reactions. TT's also inhibit DNA formation, but the mechanism has not been elucidated. TT's are mutagenic to yeast cells but are negative in mutagenicity assays using *Bacillus subtilis* and *Salmonella typhimurium*. Long-term feedings experiments with mice and rats and a long-term skin exposure study resulted in negative data regarding the carcinogenicity of TT's. (43 refs.)

- 78-0008 Short-Term Tests and Mycotoxins.** (Eng) Malaveille, C. (International Agency Res. Cancer, 150 cours Albert Thomas, 69008 Lyon, France); Bartsch, H. *Pure Appl Chem* 49(11): 1753-1757; 1977.

The uses and limitations of short-term tests for detecting adverse biological effects of mycotoxins are discussed. Different biological end-points have been proposed for the various short-term tests designed to detect potential carcinogens: DNA binding of carcinogens or their metabolites, mutagenicity, induction of DNA repair, enhancement of biphenyl-2-hydroxylase, degranulation of rat liver endoplasmic reticulum, cytogenetic alterations, and in vitro cell transformation. In many mutagenicity systems, different genetic indicators, ranging from microorganisms to mammals, are used in combination with an in vivo or in vitro activation system. The predictive value of certain test systems varies with the class of carcinogen or noncarcinogen assayed. To obtain reliable results and to overcome the specificity of one particular assay system, a battery of short-term tests is needed. In some assays, mycotoxins exert a high cytotoxic activity, preventing the testing of higher concentrations with which mutations or other DNA damage could be detected. Short-term tests have been useful in investigating the mode of action of chemical carcinogens such as aflatoxin B<sub>1</sub>. These tests are limited in that some of the factors that determine cancer development cannot be duplicated. Positive results cannot be taken to imply a definite carcinogenic activity in man. Only the probable carcinogenicity of a chemical can be predicted, without indication of the target organs. (36 refs.)

- 78-0009 More Concern over Asbestos.** (Eng) Anonymous (No affiliation given). *Chem Eng* 84(27): 28; 1977.

A recent study has detected an abnormal incidence of stomach cancer in workers exposed to the antisticking talcs used to treat finished rubber products. Workers in talc mining and milling have more significant breathing problems than coal miners, because of the release of asbestos-type fibers during these operations. The use of asbestos-emitting crushed rock in road surfacing is also being investigated. (no refs.)



- 78-0010 Here's an Update on Asbestos.** (Eng) Rajhans, G. S. (Occupational Health Branch, Occupational Health Engineering Services, Toronto, Ontario, Canada). *Occup Health Saf* 46(6): 38-43; 1977.

Existing and proposed occupational and nonoccupational standards for asbestos in the US and Canada are critically reviewed. The evolution of the time-weighted av (TWA) for asbestos exposure is outlined. With current industrial technology, a level of 2 fibers/cm<sup>3</sup> for a TWA over an 8-hr period is possible, but a proposed limit of 0.5 or 0.1 fiber/cm<sup>3</sup> suggested to be unnecessary. Furthermore, monitoring at levels of 0.1 fiber/cm<sup>3</sup> is unreliable. Exposure levels for several Canadian provinces are outlined. (28 refs.)

- 78-0011 Some New Perspectives on the Biological Effects of Asbestos.** (Eng) Rahman, Q. (Industrial Toxicology Res. Center, Post Box No. 80, Mahatma Gandhi Marg, Lucknow-226001, India); Viswanathan, P. N.; Zaidi, S. H. *Environ Res* 14(3): 487-498; 1977.

The biological effects of asbestos are reviewed, with emphasis on asbestos bodies and pleural plaques, fibrotic changes, and biomembranes as targets of toxicity.  $\alpha$ -Ketoglutarate plays a key role in the fibrogenic process. The biochemical interrelationships among the various biological effects of asbestos are depicted graphically. (95 refs.)

- 78-0012 Review of the Action of Dust Inhaled by People Working with Building Materials and by Construction Workers.** (Ger) Haublein, H. G. (Direktor des Zentralinstituts für Arbeitsmedizin der DDR, Noldnerstrasse 40-42, DDR-1134 Berlin, E. Germany). *Z Gesamte Hyg* 10(23): 709-713; 1977.

The silicoses, silicatoses, asbestoses, and malignant tumors caused by asbestos and non-specific and allergic reactions to dust inhalations are reviewed. People working with insulation materials are more susceptible to dust-induced conditions and pneumoconiosis than people in other areas of the construction industry. (58 refs.)

- 78-0013 Pathology Linked to Talc.** (Fre) Delaude, A. (Hopital Purpan, 31052 Toulouse Cedex, France). *Bull Acad Natl Med* 161(5): 405-409; 1977.

The literature on the pathogenic effects of talc is reviewed. Actually, three types of products are referred to by the term talc: chemically pure talc, which is

the silicate of magnesium hydrate; industrial talc; and commercial talc. The incidence of bronchopulmonary cancer in workers who inhale talc has been found to be 4 times that of the unexposed population. (10 refs)

- 78-0014 Health Hazards of Asbestos.** (Eng) Stacey, C. W. (Environmental Health Dept., Leicester City Council, Leicester, England); Bowman, D. R. *Environ Health* 85(11): 236-238, 235; 1977.

Long-term occupational exposure to asbestos may result in asbestosis or cancer of the bronchi, pleura, and peritoneum. The latency period for these diseases can be as long as 40 yr; minimum dose-effect relationships are not known. The risk of bronchial cancer is exceptionally high when asbestos exposure is coupled with cigarette smoking. Methods for dealing with existing asbestos health hazards are reviewed. (8 refs.)

- 78-0015 Aetiological Factors in Ovarian Cancer.** (Eng) Anonymous (No affiliation given). *Lancet* 2(8047): 1062-1063; 1977.

Several studies on risk factors in ovarian cancer indicated that it is an environmental or at least a cultural disease. Associations have been found between the cancer and unmarried women or married women with no or few children and between the cancer and menopausal estrogen intake. (16 refs.)

- 78-0016 Estrogens and Endometrial Cancer--Gross Exaggeration or Fact?** (Eng) Greenblatt, R. B. (Medical Coll. Georgia, Augusta, GA). *Geriatrics* 32(11): 60-65; 1977.

Whether or not estrogens cause endometrial cancer is controversial. This debate is complicated by the fact that some cancers regress when medication is withdrawn and are thus atypical endometrial responses to these compounds. In addition, the benefit from estrogen therapy in preventing osteoporosis in postmenopausal women far outweighs the risk of a few nonlethal endometrial cancers. To prevent any possible development of cancer in genetically prone women on estrogen therapy, they should be given a 5- to 7-day course of progestogen at monthly intervals to shed the endometrium. (30 refs.)

- 78-0017 Endometrial Hyperplasia and Carcinoma: Histopathology and Hormonal Factors.**



(Eng) Bjersing, L. (Inst. Pathology, Univ. Umea, S-901 Sweden). *Acta Obstet Gynecol Scand [Suppl]* (65): 83-88; 1977.

The role of estrogen and progesterone receptors in endometrial hyperplasia and carcinoma is reviewed. Entry of estrogens into endometrial cells is a protein-mediated mechanism and not one of simple diffusion. Estradiol-17 $\beta$  and estrone can be interconverted in the endometrial cell, with accumulation of intracellular estrone. Biological effects of various estrogens and differences that occur during different phases of the menstrual cycle are outlined. The biological effects of various estrogens are mostly determined by the strength of their binding to available cytoplasmic and nuclear receptors. The length of time the estrogen-receptor complex remains in the nucleus is critical to the biological importance of the estrogen. Studies have suggested that estriol, which is produced in high quantities during pregnancy, probably does not exert a protective influence against breast cancer. The possible role of endogenous estrone in endometrial carcinoma probably depends on the fact that estrone is the estrogen that may be chronically circulating in increased amounts, ie, in anovulatory postmenopausal patients. Progesterone, however, appears to enter the cell by simple diffusion. Since estrogens induce the growth and replication of endometrial cells and rapidly dividing cells are more likely to develop mutations, estrogens may accelerate changes leading to neoplasia. Although there are data linking estrogens, including oral contraceptives, with endometrial cancer, it is not always possible to distinguish between atypical benign hyperplasia and adenocarcinoma. Until further data are available, it is suggested that estrogens be administered only for established conditions and then only cyclically. (58 refs.)

**78-0018 Estrogens, Menopause and Cancer.** (Eng) Casey, M. J. (Dept. Obstetrics and Gynecology, Univ. Connecticut Sch. Medicine, Univ. Connecticut Health Center, Farmington, CT). *Conn Med* 41(12): 776-791; 1977.

Connecticut tumor registry data indicate that the diagnosis of uterine corpus cancer, particularly endometrial cancer, increased for women of all ages between 1953 and 1973. The pathology of these lesions and the endocrinological factors that could be involved are reviewed; exogenous estrogens have also been implicated as possible causative agents. Candidates for endometrial screening are listed, as are three methods of obtaining endometrial material for examination. (77 refs.)

**78-0019 DES Blamed for Mother's Cancers.** (Eng) Anonymous (No affiliation given). *Science News* 112(26/27): 422; 1977.

A follow-up study of women who took part in the University of Chicago's 1950-1952 diethylstilbestrol (DES) experiment indicated that the drug increases the risk of breast and other hormone-associated cancers. Compared with controls, the DES women had an excess of breast cancer (2.0 cases/100 women) and also a higher combined incidence of breast, uterine, ovarian, and colonic cancer. (1 ref.)

**78-0020 Estrogen Treatment in the Past and the Future in Cases of Estrogen Deficiency.** (Eng) Furuholm, M. (Dept. Obstetrics and Gynecology, Sabbatsberg Hosp., S-113 82 Stockholm, Sweden). *Acta Obstet Gynecol Scand [Suppl]* (65): 5-10; 1977.

The use of estrogen for the treatment of menopausal and post-menopausal symptoms is discussed. It is suggested that estrogens be administered for relief of these symptoms except in women suffering from estrogen-dependent carcinomas. It is not felt that long-term estrogen treatment would produce cancer of the endometrium or breast. (37 refs.)

**78-0021 Male as well as Female Mice Are Affected by In Utero Exposure to Diethylstilbestrol.** (Eng) McLachlan, J. A. (Environmental Toxicology Branch, Natl. Inst. Environmental Health Sciences, Washington, DC). In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, DC*. Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; 32-37; 1977.

Studies of the effect of transplacental exposure to diethylstilbestrol (DES) on the genital tracts of male and female mice are reviewed. When 16-day pregnant mice were inoculated iv with <sup>14</sup>C-DES, the compound reached the fetus within 0.5 hr and accumulated in the fetal reproductive tract. In female and male offspring of mice inoculated sc with DES on days 9-16 of gestation, DES induced a dose-related decrease in reproductive capacity. Dose-related lesions that developed in the female offspring included endometrial cystic hyperplasia and uterine adenocarcinoma. No significant lesions developed in male mice exposed to low DES doses, but 75% of those exposed to 100  $\mu$ g/kg/day DES had genital tract alterations. Testicular changes were present in 15/24 mice, and 6 had nodular enlargements of the seminal vesicle and/or coagulating gland of the prostate. In five animals, the nodular enlargements were associated with squamous metaplasia. (20 refs.)

**78-0022 Cigarette Smoking and the Lungs.** (Eng) Young, R. C. (Dept. Medicine, Howard Univ. Hosp., Washington, DC 20060). *Mt. Sinai J Med NY* 44(6): 866-872; 1977.



Since  $^{210}\text{Po}$  is found in trace amounts in cigarette smoke, this element may play a role in the development of lung cancer, mainly the squamous cell and undifferentiated types. The interaction of smoking with environmental determinants such as asbestos potentiates the development of bronchogenic carcinoma. Chronic bronchitis and airway obstruction resulting from cigarette smoke are also discussed. (23 refs.)

**78-0023 Tobacco Smolders On.** (Eng) Brody, J. S. (Boston Univ. Sch. Medicine, Boston, MA 02118). *New Engl J Med* 298(1): 48-49; 1978.

Smoking-related diseases are summarized, and recommendations are made for a multidisciplinary effort to deal with the causes of smoking. Further research on the physiology, psychology, and sociology of the smoking habit is imperative, as is the development of more effective antismoking campaigns. (11 refs.)

**78-0024 New Evidence on Smoking and Health?** (Eng) Anonymous (No affiliation given). *Med J Aust* 2(16): 515-516; 1977.

The six major points made in a paper questioning the causal relationship between cigarette smoking and lung cancer are summarized and refuted. (14 refs.)

**78-0025 New Evidence Concerning Smoking and Health.** (Eng) Sterling, T. D. (Computing Science Program, Simon Fraser Univ., Burnaby, British Columbia, Canada V5A 1S6). *Med J Aust* 2(16): 538-542; 1977.

Knowledge of the impact of airborne substances on human health has increased in the last 20 yr, especially as a result of smoking and health studies. Many sources of toxic and carcinogenic agents in air have been identified. New evidence shows the existence of a complex relationship for exposure from many sources of community pollutants as a result of occupation, smoking, and other personal habits. These pollutants, especially those encountered in blue collar occupations, account for a far larger proportion of cancers of the lung and of other sites than has been thought to be the case. (40 refs.)

**78-0026 Carcinogens in Food and Cigarette Smoke.** (Dut) Teulings, F. A. (Rotterdam, Netherlands). *Chemisch Weekblad* (43): m577; 1977.

Roasted meat and fish and the smoke generated during roasting contained large amounts of benzo(a)pyrene. When tryp-

tophan was exposed to 320-400 C, two mutagenic and possible carcinogenic compounds were formed. Cigarette smoke condensate showed a mutagenic effect. (4 refs.)

**78-0027 Physical and Chemical Processes Involved in the Production and Application of Smoke.** (Eng) Rusz, J. (Meat Res. Inst., Brno, Czechoslovakia); Miler, K. B. *Pure Appl Chem* 49(11): 1639-1654; 1977.

The tarry fraction of smokes used to preserve and flavor meat contains a high quantity of polynuclear hydrocarbons, including benzo(a)pyrene, and nitroso compounds. Nitrosamines may be included among the latter, since the wood used to produce the smoke contains 0.1%-0.32% organically bound nitrogen. At the high temperatures necessary for smoke production, the concentration of low molecular nitroso compounds is higher than that of higher boiling ones. The physical and chemical processes involved in smoke production are reviewed, and methods of controlling smoke production are outlined. (68 refs.)

**78-0028 Some Facts and Legislation Concerning Polycyclic Aromatic Hydrocarbons in Smoked Foods.** (Eng) Walker, E. A. (International Agency Res. Cancer, Lyon, France). *Pure Appl Chem* 49(11): 1673-1686; 1977.

The carcinogenic role of polycyclic aromatic hydrocarbons (PAH) in smoked foods and legislation designed to restrict their occurrence are considered. Benzo(a)pyrene has been analyzed in some vegetables, fruits, and cereals. The results indicate that the BP levels in these foods, when they are grown in the vicinity of heavy traffic, are comparable to those in smoked foods. Although evidence for the carcinogenicity of PAH in food is strong, the possibility of effects from other carcinogens, such as N-nitroso compounds, should not be neglected. Since PAH are ubiquitous in the environment and since safe background limits cannot be defined, the problem is to find a compromise between the philosophy of zero tolerance and the reality of a cost/benefit ratio. Several nations have introduced legislation to limit BP content in smoked foods and smoke flavor additives. It is concluded that adequate and reliable analytical methods for PAH are available; it must be decided which PAH should be analyzed and what levels would be tolerable in food. (35 refs.)

**78-0029 High-Pressure Liquid Chromatography: A New Technique for Studying Metabolism and Activation of Chemical Carcinogens.** (Eng) Selkirk, J. K. (Carcinogenesis Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830). In: *Environmental Cancer*. Kraybill, H.



F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): *Advances in Modern Toxicology*, Vol 3, 388 pp., 1-25; 1977.

High-pressure liquid chromatography (HPLC) has many advantages over other forms of chromatography and is ideally suited for the study of reactive intermediates in the metabolism of polycyclic aromatic hydrocarbons (PAH). HPLC gave the first unequivocal demonstration that 9-hydroxybenzo(a)pyrene was a metabolic product of benzo(a)pyrene (BP). It has been used to study the effect of enzyme inhibitors on BP metabolism and BP-DNA formation. 7,8-Benzoflavone inhibits both BP-DNA formation and diol formation, suggesting that diols are precursors to other reactive species that are also bound to DNA. In contrast, BP-DNA formation is stimulated in the presence of 1,3-epoxy-3,3,3-trichloropropane (TCPO). The fact that it also inhibits all three diols suggests that BP-DNA is formed through an epoxide intermediate and that TCPO raises the effective level of reactive epoxide by inhibiting epoxide hydase. Thereby, the amount of epoxide available for binding to DNA is increased. The HPLC patterns of BP metabolites formed by incubation of BP with human liver microsomes and human lymphocytes indicate that the epoxide hydase activity in these cells is not as rapid as that in rat cells during short-term incubations. (84 refs.)

**78-0030 Role of Analytical Chemistry in Carcinogenesis Studies.** (Eng) Burchfield, H. P. (Gulf South Res. Inst., New Iberia, LA); Storrs, E. E.; Green, E. E. *In: Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): *Advances in Modern Toxicology*, Vol. 3, 388 pp., 173-207; 1977.

The two principal roles of analytical chemistry in carcinogenesis studies are to isolate and identify potential carcinogens from environments in which cancer incidence is high and to determine if there are persistent chemicals with widespread distribution in many environments that could cause cancer in humans but at rates too low for epidemiologic detection. Use of gas-liquid chromatography (GLC) and high-pressure liquid chromatography combined with gas-phase and liquid-phase spectrofluorometry can be used to determine nanogram quantities of most mixtures isolated from the environment. The structure of most organic compounds can be determined with the combined results obtained by infrared, mass, and nuclear magnetic resonance spectrometry. In carcinogenicity bioassays, analytical chemistry provides information on the chemicals being tested, doses administered, and interactions with test animals. The combination of GLC plus mass spectrometry is valuable in metabolic studies, making it possible to identify and detect compounds at very low levels. Modern analytical techniques can follow the conversion of proximate carcinogens to ultimate carcinogens and they can measure body burden, a key measurement in relating dose to biological response. (48 refs.)

**78-0031 Ames Test Success Paves Way for Short-Term Cancer Testing.** (Eng) Fox, J. L. (Chemical Engineering News, 1155 16th St., NW, Washington, DC). *Chem Eng News* 55(50): 34-36, 42, 44-46; 1977.

The Ames *Salmonella typhimurium* assay and other short-term screening tests for chemical carcinogens and mutants are evaluated. Data are presented on the carcinogenicity of saccharin as evaluated by a battery of tests, including the Ames assay; the Pol test with DNA repair-deficient bacteria; the Drosophila test; tests using unscheduled DNA synthesis, sister chromatid exchange, mutations in cultured mammalian cells, and animal cell transformation; and the plasminogen activator test. (no refs.)

**78-0032 Chemical Carcinogenesis: An Emerging New Perspective.** (Eng) Farber, E. (Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada); Solt, D.; Cameron, R.; Laishes, B.; Medline, A. *In: Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan) 441 pp; 429-438; 1977.

A review of cancer induction in different species and organs with different carcinogens reveals many superficial similarities. Comparison of carcinogenesis in the rat liver (an organ with little cell renewal) with that in mouse skin (an organ with a high rate of cell renewal) reveals striking similarities in the overall pattern of the process. The first step is the induction of a rapid irreversible change that could be a somatic mutation. The fate of the altered cells depends on the local tissue environment. Some promotional event is necessary to favor their proliferation over normal cells. The development of neoplasia from these initiated cells resembles the differentiation or maturation of committed fetal cells, but the initiated cells cannot reproduce the normal processes of development and maturation. Despite this, if they are stimulated to proliferate, the majority of these cells show maturation to normal-appearing tissue. However, some foci of altered cells do not show maturation and these seem to be precursors to neoplasia. Fetal markers, which may occur early in carcinogenesis, are indicative of the reversion to a fetal-like cell from which cancer develops. It is suggested that there are a minimum number of patterns in chemical carcinogenesis and that the same patterns apply to irradiation and viral-induced carcinogenesis. (17 refs.)

**78-0033 Hepatocarcinogenesis by Chemicals.** (Eng) Miller, E. C. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI); Miller, J. A. *Prog Liver Dis* 5:699-711; 1977.



The current knowledge of chemical hepatocarcinogenesis at the molecular level is reviewed. The hepatocarcinogens considered include aromatic amines and amides, halogenated aliphatic and alicyclic compounds, polycyclic aromatic hydrocarbons, alkyl nitrosamines and alkyl nitrosamides, and aflatoxin B. The subjects covered are the gross changes induced in liver cells by the carcinogens, the metabolic activation of the chemicals, critical molecular targets, and the genetic and epigenetic theories of tumor induction. It is emphasized that the basic principles of the metabolic activation of hepatic carcinogens are now known and that interactions of ultimate carcinogens with liver cell constituents are becoming better-defined. Epidemiologic studies should provide additional information on the role of chemical carcinogens in human liver cancer. (70 refs.)

- 78-0034 **Conceptual Approaches to the Assessment of Nonoccupational Environmental Cancer.** (Eng) Kraybill, H. F. (NCI, NIH, Bethesda, MD 20014). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 3, 388 pp., 27-62; 1977.

The assessment of carcinogenic risks for the general population is facilitated by studies with experimental animals and by retrospective and prospective studies of specified human populations. Criteria are needed for evaluating the predictive value of animal data for human cancer; some efforts are being made in this direction through national and international advisory bodies. The types of exposures received by an individual from his environment are multiple and, thus, they present a multiple risk. More studies are needed to evaluate the effect of mixed agents and to test their synergistic and/or inhibitory role. The design is difficult, but certain matrices, providing for the simultaneous testing of at least 12 chemicals, are available. An alternative approach to the evaluation of carcinogenic risk would be to consider the combined effect of the environmental chemicals to which humans are exposed. This approach could first be explored by determining the biological response of total extracts and subfractions of extracts of polluted water, polluted air, and contaminated diets. In a comprehensive evaluation of the environmental cancer problem, all of the data bases available from experimental oncology, environmental monitoring and surveillance networks, and observations on neoplasia in marine and terrestrial animals must be utilized and correlated with observations in human population. (88 refs.)

- 78-0035 **Nutrition and Experimental Carcinogenesis.** (Eng) Clayson, D. B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB). *Curr Concepts Nutr* 6: 15-23; 1977.

The effects of nutritional modifications on experimental carcinogenesis are reviewed with emphasis on calorie restriction, protein levels, lipotrope deficiency, lipids, and vitamin A and vitamin C. Nutritional variables should be controlled strictly, since their effects can occur at one of the following phases in carcinogenesis: (1) detoxification or conversion of a carcinogen to its active form; (2) binding of the carcinogen to its cellular target; or (3) the development of a clinically observable tumor. (38 refs.)

- 78-0036 **Toxicology in Cancer Research.** (Eng) Schmahl, D. (Institut für Toxikologie und Chemotherapie am Deutschen Krebsforschungszentrum, Im Novenheimer Feld 280, 69 Heidelberg, W. Germany). *Interdisciplinary Sci Rev* 2(4): 305-311; 1977.

The role of toxicology in cancer research is reviewed. A study of occupational and geographic cancers indicated that there is a high prevalence of gastric cancer in Japan and a dietary factor in the etiology. It also implicated vinyl chloride in hemangiosarcoma induction and haloethers in the development of carcinomas of the bronchi. Natural products may also be carcinogenic. Certain or probable natural carcinogens include aflatoxins, arsenic, asbestos, betel nuts, *Cycas circinalis*, *Pteris aquilina*, pyrrolicidin alkaloids, Streptozotocin, and tobacco. In testing substances for carcinogenicity, species with responses similar to those of humans must be found. In addition, prenatal toxicological effects must be considered. An example of this is diethylstilbestrol-induced vaginal adenocarcinomas in daughters of women who took the drug. Various drugs used in cancer therapy are also known carcinogens (alkylating agents, arsenic, diethylstilbestrol, and procarbazine), but in many cases their benefits outweigh their adverse effects. Future toxicological research should focus on measures of reducing the toxic side effects of many cancer therapy drugs. It is generally thought that chemical carcinogens work by attacking genetic material. Carcinogens differ with respect to their dose-effect and dose-time relationships. (37 refs.)

- 78-0037 **Substances Carcinogenic to Man?** (Ger) Schramm, T. (Bereich Chemische Kanzerogenese, Zentralinstitut für Krebsforschung der AdW der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany); Teichmann, B. *Z Gesamte Hyg* 21(11): 847-850; 1977.

All chemical compounds found to be carcinogenic in bioassays should be regarded as dangerous to man until proved otherwise; no distinction should be made between animal and human carcinogens. Suggestions for protecting humans from these compounds are outlined. (24 refs.)



**78-0038 Use of Statistics when Examining Lifetime Studies in Rodents to Detect Carcinogenicity.**

(Eng) Salsburg, D. S. (Dept. Clinical Res., Pfizer Central Res., Eastern Point Road, Groton, CT 06340). *J Toxicol Environ Health* 3(4): 611-628; 1977.

The lifetime feeding assay for carcinogenicity that subjects groups of 50 animals per sex per dose to each of three doses with a comparable number of controls was examined for its statistical properties. Using the standard formulation of tests of hypothesis, it is shown that there is a 20%-50% chance of a false positive and that it is possible to define a weak carcinogen in terms of the degree of effect that would produce a false negative < 5% of the time. Whether hypothesis testing is a proper use of statistics in this context is questioned, and alternatives are proposed. (17 refs.)

**78-0039 Reflections on the Art of Bioassay for Carcinogenesis.**

(Eng) Shimkin, M. B. (Dept. Community Medicine, Univ. California at San Diego, La Jolla, CA). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 3, 388 pp., 373-381; 1977.

Factors involved in developing bioassay systems for carcinogenicity testing are discussed. All bioassays involve the material to be tested and the biological system on which the test is to be performed. Both should be as stable as possible and be kept under stable environmental conditions. The end point of the test should be defined quantitatively. The choice of the animal depends upon the purpose of the experiment, and it is determined by available information and available stocks. The administration route and schedule and similar factors must be individualized to the requirements of the investigations. The end point of carcinogenesis testing on animals is the appearance of malignant neoplasms, preferably without their appearance among untreated controls. Induction, therefore, is inferred, although the induced tumors usually represent the earlier appearance of tumors encountered spontaneously at later times and in smaller numbers among the untreated population. The results of bioassay testing should permit one to classify the chemicals tested according to the predominant tissue in which the carcinogenic response is elicited, according to whether they are rapidly acting or weak carcinogens, and according to specificity of the reaction with regard to species or specialized conditions. Biometric design of bioassay experiments, including the analysis and presentation of results, is necessary. (23 refs.)

**78-0040 Concepts of a Bioassay Program in Environmental Carcinogenesis.**

(Eng) Page, N. P. (NCI, NIH, Bethesda, MD 20014). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 3, 388 pp., 87-171; 1977.

Current concepts of the NCI bioassay program, primarily those pertaining to long-term in vivo animal tests, are presented with special emphasis on the screening assay for carcinogenicity. Chemicals selected for long-term animal bioassay are those believed to have immediate or potential human exposure of such magnitude that human exposure would be restricted should they prove carcinogenic in animal tests. NCI has developed carcinogenicity test guidelines covering the test animals, chemistry, route of administration, doses and dose levels, treatment period, sample size, pathology examination, and data reporting. Personnel exposures to chemicals that have not yet been tested must be minimized as much as possible through effective containment and safe work practices. (128 refs.)

**78-0041 Cancer Prevention.**

(Eng) Weisburger, J. H. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595). *Chemtech* 7(12): 734-740; 1977.

Cancer accounts for approx 17% of all deaths in the US, 80%-90% of which are due to environmental factors. Most of these factors are made by man and thus can be prevented by man. The estimated cancer deaths by sex for all sites in 1975 and the percentage of cancers at selected sites for which there are sound etiologic hypotheses are tabulated. A general discussion of chemical carcinogens and threshold levels, occupational cancer, and radiation-induced cancer is included. Most cancers stem from factors other than occupational exposure. They are the life-style-related cancers, causally related to cigarettes, and to personal dietary habits. Recommended means of preventing the life-style-related and occupational cancers are listed. (18 refs.)

**78-0042 Inhibition of Chemical Carcinogenesis.**

(Eng) Wattenberg, L. W. (Dept. Lab. Medicine and Pathology, Medical Sch., Univ. Minnesota, Minneapolis, MN 55455). *J Natl Cancer Inst* 60(1): 11-18; 1978.

The inhibition of chemical carcinogenesis by compounds which alter metabolism, scavenge the active species, or competitively inhibit the carcinogen is discussed. These inhibitors include phenolic antioxidants like butylated hydroxyanisole and butylated hydroxytoluene, ethoxyquin, disulfiram and related compounds, organic isothiocyanates, organic thiocyanates, lactones like coumarin and  $\alpha$ -angelicalactone, selenium salts, inducers and inhibitors of microsomal mixed function oxidase activity, and physiologic trapping agents like glutathione. The deliberate use of inhibitors to reduce cancer incidence is discussed. (62 refs.)

**78-0043 Controlling Cancer in the Workplace.**

(Eng) McGinty, L. (No affiliation given). *New Sci* 76(1083): 758-761; 1977.



Policy differences between the US and UK with respect to the determination of carcinogens and regulation of their exposure are outlined. In the US, positive carcinogenicity results in animal studies are sufficient to warrant reduction or elimination of human studies are exposure to the chemical. In the UK, however, results of animal studies are not sufficient evidence for withdrawal of the chemical from the market. Human epidemiological studies are also necessary. Furthermore, the tentative scheme for handling carcinogens in the UK focuses on minimizing exposure to known carcinogens. The US, on the other hand, follows the no-threshold theory and attempts to keep exposure as low as possible. It is suggested that differences in the strengths and priorities of the unions in the US and UK are responsible for the different approaches. (no refs.)

**78-0044 Occupational Carcinogenesis.** (Eng) Lassiter, D. V. (Center Occupational and Environmental Safety and Health, Stanford Res. Inst., Menlo Park, CA). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 3, 388 pp., 63-86; 1977.

The control of occupational cancer in the US on the part of employers has been stimulated recently by the 1970 Occupational Safety and Health Act. Regulation of carcinogenic chemicals in the workplace may include a ban of production and/or use, mandatory substitution whenever possible, or limitation of exposure to within prescribed limits. Employee exposure to potential carcinogens should be controlled by reducing ambient concentrations to safe levels. Although epidemiologic investigations and animal experimentation are the two primary sources of evidence necessary to establish the etiology of occupational cancers, the impact of information from these sources on the development of control measures often has been less than substantial. New questions of employer responsibility will probably be raised concerning legal liability for exposing employees even to unregulated substances when the employer has reason to believe that this exposure may be hazardous. Occupational carcinogenic chemicals should be classified to determine priorities for evaluation, followed by bioassay testing and epidemiologic investigations to establish tumor etiology with certainty. (24 refs.)

**78-0045 Testing of Industrial Chemicals.** (Eng) McLean, A. E. (Lab. Toxicology, Dept. Clinical Pharmacology, Univ. Coll. Hosp. Medical Sch., London WC1E 6JJ, England). *Lancet* 2(8047): 1070-1071; 1977.

The question is raised as to whether the United Kingdom's Health and Safety Commission and its Executive are performing the right tests on potentially dangerous industrial compounds. Proper testing involves assessment of toxicity, hazards relating to the method of exposure, and benefits obtained vs risk and an epidemiological follow-up. (4 refs.)

**78-0046 Introduction (Symposium on the Stability of the Neoplastic State).** (Eng) Pitot, H. C. (No affiliation given). *Am J Pathol* 89(3): 667-670; 1977.

Studies of the two-step model of neoplastic transformation have shown that tumor initiators act rapidly and that the effect is permanent (although new data have indicated that it can be modulated or reversed). Tumor promoters, however, may be influenced by dietary or hormonal factors, age, frequency of exposure, and time of exposure relative to that of the initiator. (13 refs.)

**78-0047 Carcinogenic Polycyclic Aromatics and Metabolites as Possible Components of Emissions.** (Ger) Herlan, A. (Engler-Bunte-Institut, Bereich Gas, Erdol und Kohle, Universitat Karlsruhe, Richard Willstätter-Allee 5, D-7500 Karlsruhe, W. Germany). *Zentralbl Bakteriol [Orig B]* 165(2): 174-191; 1977.

Empirical and structural molecular formulas of the carcinogenic polycyclic aromatic hydrocarbons metabolites found in light fuel oil, dusts from highways and towns, and emissions from oil ovens are presented. (24 refs.)

**78-0048 Genetic Effects Associated with Industrial Chemicals.** (Eng) Wagoner, J. K. (Industrywide Studies Branch, Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH); Infante, P. F.; Brown, D. P. In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C.* Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; 100-113; 1977.

The carcinogenicity and mutagenicity of various chemicals found in the workplace are reviewed, with emphasis on their genetic effects. Women have been excluded from workplaces where vinyl chloride (VC) may be inhaled, but studies have also shown an increased fetal death rate in the offspring of men exposed to VC. Two structural analogs of VC, vinylidene chloride and trichloroethylene, which have wide industrial use, have been shown to be carcinogenic in rodents and mutagenic in microbial and plant assays. However, human data for both are lacking. Functional disruption of spermatogenesis occurred among men occupationally exposed to chloroprene (2-chlorobutadiene) for  $\leq 10$  yr, and morphological disruption of spermatogenesis occurred among men exposed for  $> 10$  yr. Wives of workers exposed to chloroprene have a threefold excess of miscarriage. (38 refs.)

**78-0049 Birth Defects and Vinyl Chloride.** (Eng) Edmonds, L. (Birth Defects Branch, Center Disease Control, Atlanta, GA). In: *Proceedings Conference on*



*Women and the Workplace, June 17-19, 1976, Washington, D. C. Society for Occupational and Environmental Health (Washington, D.C.): 364 pp.; 114-119; 1977.*

A review of CNS birth defects in two cities that have vinyl chloride (VC)-producing plants revealed that the defect rates were higher than expected but they were not significantly different from the US rates at that time. There was no statistically significant excess of defects in offspring of men who worked at the plant, or of families residing near the plant. (no refs.)

**78-0050 Occupational Cancer: Government Challenged in Beryllium Proceeding.** (Eng) Shapley, D. (No affiliation given). *Science* 198(4320): 898-899, 901; 1977.

A controversial paper linking beryllium exposure with increased incidence of lung cancer is discussed. Arguments are presented that the increased number of deaths may be due to other factors and that the statistics are difficult to verify because of incomplete information due to poor record-keeping by the beryllium industry. (no refs.)

**78-0051 Inorganic Agents as Carcinogens.** (Eng) Furst, A. (Inst. Chemical Biology, Univ. San Francisco, San Francisco, CA). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 3, 388 pp., 209-229; 1977.

Metal carcinogenesis is reviewed under three main categories: metals for which there are animal data supported by human evidence, metals active in animals with no supporting human evidence, and metals claimed to be carcinogenic without sufficient evidence. Nickel and a variety of nickel compounds (nickel subsulfide, nickel acetate) are carcinogenic in animals and in man (cancer of the nasal cavity and lung). Calcium chromate induces skin and lung cancer in chromate workers, but few tumors have been induced in animals. There is no conclusive epidemiological evidence that exposure to cadmium, lead, or beryllium leads to an increased tumor incidence, but some investigations of human carcinogenesis suggest that this may be the case. These metals and/or their compounds have induced tumors in animals. Zinc, cobalt, and iron have been reported to be carcinogenic by various investigators, but the supporting data are still not sufficient. There is good epidemiological evidence to implicate arsenic as a cause of skin cancer, but repeated attempts to induce any type of neoplasm in animals have been unsuccessful. Conflicting results exist on the ability of selenium to induce tumors in experimental animals; a major factor may be diet. Little work has been done on the mechanisms of action of metal. There is evidence, however, that metals are reactive and dissolve rap-

idly in the animal body. By some unknown means, they also enter cells and are distributed in an orderly fashion. (206 refs.)

**78-0052 The Effects of Lead on Reproduction.** (Eng) Infante, P. F. (Industrywide Studies Branch, Div. Surveillance, Hazard Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH); Waggoner, J. K. In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C. Society for Occupational and Environmental Health*. (Washington, D.C.): 364 pp.; 232-242; 1976.

In addition to respiratory and kidney cancers in animals exposed to lead, human epidemiological data have indicated increased incidences of these cancers in lead workers and residents of areas containing lead smelters. Evidence of the mutagenic and teratogenic effects of lead in humans and animals is outlined. Male as well as female exposure to lead may be a factor in mutagenesis and teratogenesis. (41 refs.)

**78-0053 Modulation of the Expression of the Cancer Cell Phenotype.** (Eng) Weinstein, I. B. (Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 65-67; 1977.

Among the factors that modulate reversibly the cancer cell phenotype, phorbol esters induce plasminogen activator synthesis, alter cell-surface glycopeptides of cultured tumor cells, and further potentiate the expression of the transformed phenotype. In normal cells, the esters induce changes that mimic the properties of transformed cells. In contrast, glucocorticoids induce phenotypic changes in cancer cells so that their growth properties resemble those of normal cells. Studies with temperature-sensitive mutants of transformed rat epithelial cells provide additional examples of the reversible modulation of the transformed phenotype. (9 refs.)

**78-0054 Cell Culture Studies Provide New Information on Tumour Promoters.** (Eng) Weinstein, I. B. (Dept. Medicine, Coll. Physicians and Surgeons, Columbia Univ., New York, NY); Wigler, M. *Nature* 270(5639): 659-660; 1977.

Studies of the action of the most potent known tumor-promoting agents, the phorbol diesters, in cell culture are



reviewed. Nanomolar concentrations of these esters induce changes in cultured cells that resemble those seen upon transformation with either chemical carcinogens or tumor viruses. They also further enhance the expression of these transformation-specific phenotypic features in already transformed cells. In chicken embryo fibroblasts, phorbol esters alter cellular morphology, increase plasminogen activator synthesis, alter the composition of glycopeptides obtained from cell membranes, increase deoxyglucose uptake, and cause loss of the large external transformation-sensitive (LETS) protein. Phorbol esters also reversibly inhibit terminal differentiation, as observed in chicken embryo myoblasts undergoing myogenesis, in Friend erythroleukemia cells undergoing spontaneous or induced erythroid differentiation, in the differentiation of neuroblastoma cells in culture and of 3T3 cells to lipocytes, and in the chondrogenesis of chicken embryo chondroblasts. Study of the cellular and molecular bases for the action of the phorbol esters may suggest novel approaches to the control of neoplasia. (19 refs.)

**78-0055 Artificial Sweeteners and Bladder Cancer (Letter to Editor).** (Eng) Miller, A. B. (Epidemiology Unit, Natl. Cancer Inst. Canada, Univ. Toronto, Toronto, Ontario, Canada); Howe, G. R. *Lancet* 2(8050): 1221-1222; 1977.

The Canadian study that found a positive association between artificial sweeteners consumption and male bladder cancer is reviewed. Topics include selection of controls according to matched and unmatched variables and differences in sweetener use for men and women. If the observed association between artificial sweeteners and male bladder cancer is not due to chance, then it must be (1) real, (2) due to confounding, or (3) due to bias or error in study design and execution. The study of the last two being true is discussed. (11 refs.)

**78-0056 Health Effects of Organics: Risk and Hazard Assessment of Ingested Chloroform.** (Eng) Tar-diff, R. G. (Board on Toxicology and Environmental Health Hazards, Natl. Acad. Sciences, Washington, DC). *Am Waterworks Asso J* 68(12): 658-661; 1977.

Experimental data on chloroform carcinogenicity are reviewed, and their importance to man is discussed. In mice, 30 po doses of 0.4 or 0.8 ml/kg produced nonmetastasizing hepatomas and cirrhosis; however, a single sc injection of 200 µg chloroform was not carcinogenic. When Osborne-Mendel rats and B6C3F1 mice were given two doses of 90-200 mg/kg or 138-477 mg/kg, respectively, five times per week for 78 wk, kidney tumors resulted in male rats, liver tumors in male and female mice. There was a dose-related response in the animals developing tumors. Extrapolation of these findings to man is difficult and is complicated by the fact that there

is no epidemiological evidence implicating chloroform as a human carcinogen. The problems of extrapolating from high- to low-dose levels and several methods of estimating risk are outlined. It is suggested that human exposure (via tap water) should not exceed 0.01 mg/kg/day (or 70 ppb). Chloroform exposure could account for as much as 1.6% of the liver cancer and 1.44% of the renal cancer incidence each year. It is estimated that 252/approx 300,000 cancer deaths each year are the result of chloroform in the tap water. (10 refs.)

**78-0057 Hair Dyes and Cancer: "Screening Tests" Are Not Relevant. Parts 1 and 2.** (Eng) Burton, D. (No affiliation given). *Soap Perfum Cosmet* 50(10): 410-413, 415, 417, 419 and 50(11): 471, 473, 475, 477; 1977.

Studies of the possible carcinogenicity of hair dyes are reviewed, with emphasis on the use of screening tests to detect mutagens. The belief that mutagenic chemicals are carcinogenic is based on the results of tests of 300 chemicals (including 174 known carcinogens) in the Ames Salmonella mutation assay. Of these, 156 were mutagenic. Few of the noncarcinogens were mutagenic. Although this work merits serious consideration, other evidence must be considered, particularly the fact that the mutagenic aromatic amines used in hair dyes have not produced cancer in experimental animals. Epidemiological studies have also linked exposure to chemicals, including dyes, to various types of cancer. Other studies using Ames-positive dyes that were injected, fed, or applied to the skin have failed to show an association between hair dyes and cancer. It is concluded that screening tests, specifically the Ames test for bacterial mutations, have no significance for human cancer. (97 refs.)

**78-0058 Carcinogenicity of Dyes (Letter to Editor).** (Eng) Kay, K. (Mount Sinai Sch. Medicine, Mount Sinai Medical Center, New York, NY). *Textile Chemist Colorist* 9(11): 44-45; 1977.

Evidence from various sources on the carcinogenicity of dyes and inks is reviewed. Early evidence of bladder cancer in dye workers was linked to chemicals such as  $\beta$ -naphthylamine, benzidine, and 4-aminobiphenyl and other intermediates. Even though levels were reduced and safeguards established, the wide variety of coloring agents available preceded rapid mutagenicity testing. Bladder cancer was also linked with textile, leather, and rubber workers. A review of 37 materials used in graphic arts revealed only 4 carcinogens, but 15 belonged to chemical classes in which carcinogens had been identified. Furthermore, benzene and trichloroethylene, known carcinogens, have been used as solvents in graphic arts operations. A recent Russian study on bladder cancer sup-



ported the higher than normal incidence in textile workers exposed to dyes containing carcinogenic radicals. Use of the Ames mutagenicity test on 19 printing ink constituents revealed 2 to be mutagenic. There is no comprehensive directory on the range of colorants used in textile finishing. A study should be made to evaluate the three main sources of exposure: dye formulation, textile dyeing, and inhalation and absorption of dye-impregnated textiles through wear. (32 refs.)

- 78-0059 Organohalogen Carcinogens.** (Eng) Burchfield, H. P. (Gulf South Res. Inst., New Iberia, LA); Storrs, E. E. In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol.3, 388 pp., 319-371; 1977.

Alkylating agents can cause mutations and cancer, and many organohalogen compounds are alkylating agents. Oxygenated alkyl halides, depending on the position of substitution, are generally more powerful alkylating agents and mutagens than the unsubstituted compounds. The reasons for the carcinogenicity of chlorinated hydrocarbon insecticides to rodents are not known. These compounds are not strong alkylating agents, and comparisons of the influence of chemical structure on insecticidal activity indicate that molecular configuration is probably far more important than chemical reactivity. Conceivably, some of these compounds could be converted to alkylating agents by enzymatic dehydrochlorination, dechlorination, and/or epoxidation. Fungicides that contain halogen atoms activated by adjacent quinone, nitrile, nitro, and heterocyclic groups are powerful alkylating agents. However, some of these compounds may be detoxified rather than activated before they reach genetically vulnerable sites and they appear to be of relatively low carcinogenic activity. Mutagenicity correlates well with carcinogenicity for many groups of compounds, but not organohalogen compounds.  $\text{CHCl}_3$ , carbon tetrachloride, dieldrin, and other chlorinated hydrocarbon insecticides are carcinogenic to mice, but they are not mutagenic when tested by currently available methods. (124 refs.)

- 78-0060 Cancer, Miscarriages and Birth Defects Associated with Operating Room Exposure.** (Eng) Corbett, T. H. (US Veterans Admin. Hosp., Ann Arbor, MI). In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, DC*. Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; 94-99; 1977.

The risks associated with occupational exposure to anesthetic gas (eg, halogenated hydrocarbons and halogenated ethers) are discussed. A nationwide survey of 50,000 operating room professionals found that the incidence of spontaneous abor-

tions was 1.3-2 times higher in exposed than in unexposed personnel. Physician-anesthetists had the highest risk, followed by nurse-anesthetists. The incidence of congenital abnormalities among children of female physician-anesthetists was double that among children of unexposed female physicians. For nurse-anesthetists, the risk of fetal abnormalities was 1.6 times that of their unexposed counterparts. There was also a 25% increase in the risk of congenital abnormalities in children of male anesthesiologists. An excess cancer incidence was noted among the exposed women. Liver disease, excluding serum hepatitis, was also more frequent among exposed women than among their unexposed counterparts and among male physician-anesthetists compared with male pediatricians. The use of scavenging devices to reduce operating room levels of anesthetic gases is suggested. (3 refs.)

- 78-0061 Drug-induced Gastrointestinal Disease.** (Eng) Hyson, E. A. (Dept. Diagnostic Radiology, Yale Univ. Sch. Medicine, New Haven, CT 06510); Burrell, M.; Toffler, R. *Gastrointest Radiol* 2(3): 183-212; 1977.

A comprehensive review of drug-induced gastrointestinal diseases and their radiographic manifestations is presented. Descriptions of benign and malignant liver tumors induced by oral contraceptives are included. (275 refs.)

- 78-0062 Nitrosamines and Nitrosamides in the Etiology of Gastrointestinal Cancer.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701). *Cancer [Suppl]* 40(5): 2446-2449; 1977.

N-Nitroso compounds are formed by the interaction of nitrate with secondary and tertiary amino compounds, a reaction that can occur in vivo as well as in food processed with nitrite. The favored site of reaction in vivo is the stomach. N-Nitroso compounds formed in this way, especially nitrosamides, could reach the colon and contribute to the induction of colon tumors. (25 refs.)

- 78-0063 Current Views on Mechanisms Concerned with the Etiology of Cancers in the Digestive Tract.** (Eng) Weisburger, J. H. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY). In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 1-20; 1977.



The etiology of cancer of the digestive organs is discussed. In the past 40 yr, an increase in fat intake in the US has been accompanied by an increase in colon cancer. Furthermore, bacteria that produce secondary bile acids are present in higher quantities in the stools of high-risk subjects than in those of low-risk subjects. Parallel results were obtained in animal studies, in which it was also shown that bile acids have a promotional effect on colon cancer in conventional and germ-free animals. This suggests that these acids are involved in human colonic cancer. An association has also been postulated among diet, smoking, and pancreatic cancer. As with colonic cancer, it is fat intake in the diet that is implicated. Examination of gastric cancer indicates that nitrite-containing foods appear to have an etiological role. These nitrites are either added as preservatives or they are from foods grown in soil with high nitrite levels. Furthermore, populations at risk for gastric cancer usually eat a diet containing high levels of carbohydrates and salts, and limited micronutrients especially vitamin C. Vitamin C has been shown to prevent mutagen formation from nitrite under similar human gastric conditions. It may also prevent the formation of carcinogenic alkylnitrosamides from nitrites. (47 refs.)

- 78-0064 What Is The Relationship of Cancer to Aging?**  
(Eng) Kent, S. (No affiliation given). *Geriatrics* 32(11): 113-114, 119, 122; 1977.

Application of 7,12-dimethylbenz(a)anthracene to the skin of BALB/c mice induces more tumors in older animals than in younger ones. This could be related to a decreased chalone content in senescent skin or to possible defects in excision repair. However, an increased susceptibility in younger animals compared to middle-aged animals could be due to a higher mitotic rate. Thus, cellular factors could play a role in the increased cancer incidence in humans with age. Immunosurveillance defects and hormonal composition may also predispose an individual to cancer. (36 refs.)

- 78-0065 Bone Marrow Depressant and Leukemogenic Actions of Benzene.** (Eng) Synder, R. (Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA 19107); Lee, E. W.; Kocsis, J. J.; Witmer, C. M. *Life Sci* 21(12): 1709-1722; 1977.

Chronic benzene toxicity is expressed as bone marrow depression resulting in leukopenia, anemia, or thrombocytopenia. Prolonged exposure results in disease progression from bone marrow aplasia to pancytopenia. Experimental data linking occupational exposure to benzene with leukemias are reviewed, and it is suggested that leukemia is as frequent a cause of death from chronic benzene exposure as is aplastic anemia. Both the stimulation and inhibition of benzene metabolism

protect against the toxic action of the compound. Evidence points to production of a specific metabolite, possibly in the bone marrow, as the cause of toxicity. Although the exact nature of this metabolite is unknown, it may be benzene epoxide. There is no evidence that benzene metabolites formed in the liver are transported to the bone marrow. (96 refs.)

- 78-0066 Reversal of the Neoplastic State in Plants.**  
(Eng) Meins, F. (Dept. Botany, Univ. Illinois, Urbana, IL 61801). *Am J Pathol* 89(3): 687-702; 1977.

Factors underlying the progression and reversal of crown-gall tumors in plants are reviewed. The plasmid and epigenetic hypotheses of transformation are discussed, together with the nutritional requirements of normal and tumor cells in culture. Conversion of a cell division factor (CDF)-requiring normal cell to the CDF autotrophic state is a key event in transformation. The fact that CDF habituation is progressive, occurs in the absence of agents of bacterial origin, and has an epigenetic basis indicates that neither somatic mutation nor the addition of foreign genes accounts for tumor stability and progression in crown-gall disease. This conclusion supports the hypothesis that cancer is basically a problem of anomalous differentiation arising from epigenetic modifications of the cellular genome. (78 refs.)

- 78-0067 Oncogenicity of Cycads and Its Implications.**  
(Eng) Laqueur, G. L. (Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014). In: *Environmental Cancer*. Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 3, 388 pp., 231-261; 1977.

Studies of the oncogenicity and other adverse properties of cycads, which are widely used as a source of medicine and food, are reviewed. During the preparation of cycad starch as food, the toxic substance is removed. There have been no reports of an increased cancer incidence in populations eating cycad material. Early studies with cycads indicated that the glycoside cycasin and its aglycone, methylazoxymethanol (MAM), shared many of their biologic effects with dimethylnitrosamine (DMN). These similarities are thought to be due to the formation of a highly reactive common metabolite, most likely methyl carbonium hydroxide, during the decomposition of MAM and DMN. This metabolite serves as the methyl donor, ultimate carcinogen, mutagen, and teratogen. Experiments with rats indicate that the toxicologic and oncogenic effects of cycad glycosides occur only when they are hydrolyzed; this hydrolysis in the gut results from and depends on an intestinal microflora. Tumor induction in rats by cycads has been successful in all strains used. The most frequently reported tumors occur in the liver, kidney, colon,



lung, brain, and duodenum. Occasional neoplasms are formed in the small intestine, ear canal, renal pelvis, and urinary bladder, or they arise from the peripheral nerves. Oncogenic effects of cycads have also been reported in mice, hamsters, guinea pigs, and fish. (31 refs.)

- 78-0068 Multiple Simultaneous Event Model for Radiation Carcinogenesis (Letter to Editor).** (Eng) Morgan, K. Z. (Sch. Nuclear Engineering, Georgia Inst. Technology, Atlanta, GA 30332); Cattell, F. C.; Cook, J. E. *Health Phys* 33(4): 347; 1977.

Baum's multiple simultaneous event model for radiation carcinogenesis fails to take into account cells converted from state 0 to state 2 during irradiation. These cells are also available for further conversion to state 4. When only cells originally in state 2 can proceed to state 4, the model fits; however, when the cells entering state 2 during exposure are included, a better fit results with the assumption of triple or quadratic steps, and not double ones. It is concluded that the claims made for the predictive power of the model are unacceptable. (1 ref.)

- 78-0069 Can Breast Cancer Be Radiation Induced?** (Eng) Feig, S. A. (No affiliation given). In: *Breast Carcinoma: The Radiologist's Expanded Role*. Logan, W. W., ed. (New York: John Wiley & Sons): pp. 5-14; 1977.

Radiation has been implicated as a cause of breast cancer in women treated for tuberculosis by artificial pneumothorax and multiple fluoroscopies, women treated by radiotherapy for postpartum mastitis, and Japanese women exposed to the atom bomb. Risk estimates of breast cancer at high and low radiation doses are presented, along with calculations of the benefit/risk ratios of mammography. (20 refs.)

- 78-0070 Radiation Exposure and Protection.** (Eng) Hunt, V. R. (Dept. Environmental Health, Pennsylvania State Univ., Univ. Park, PA). In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C.* Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; 196-201; 1977.

According to the National Council on Radiation Protection and Measurements, there is no threshold radiation dose, and all exposures should be kept as low as possible. Nevertheless, one max allowable standard has been set. For pregnant women, total fetal exposure should not exceed 0.5 REM (radia-

tion-equivalent-man) for the entire gestation. More studies of the effects of radiation on fertility, ie studies of x-ray technicians and nurses exposed to radiation, are needed. Studies of sperm are also needed to determine if they accumulate other elements besides polonium. Although the placenta has been shown to be relatively radioresistant, any detoxifying capacities it may have are not known. (no refs.)

- 78-0071 The Continuing Body Count at Hiroshima and Nagasaki.** (Eng) Barnaby, F. (Stockholm International Peace Res. Inst., Stockholm, Sweden). *Bull At Sci* 33(10): 48-53; 1977.

Physical data on the atomic bombs and their effects in Hiroshima and Nagasaki are reviewed. Within 10 yr of the blast, leukemia mortality increased, reaching a level 30 times higher than the national av; it still has not fallen to the national av. The incidence of malignant thyroid, breast, lung, salivary gland, prostate, and bone tumors is still higher in the exposed populations than in nonexposed persons. The most common congenital abnormality was microcephaly. Surprisingly, no increased incidence of leukemia has been reported for children exposed in utero, and, apparently, there was no genetic damage to survivors exposed to radiation. (no refs.)

- 78-0072 Enhancement of Pigmentation: Psoralens.** (Eng) Dawber, R. P. (Radcliffe Infirmary, Oxford, England). *J Soc Cosmet Chem* 28(7): 403-406; 1977.

The mode of action of psoralens (eg, 4-methylpsoralen and 4,5',8-trimethylpsoralen) and their effectiveness in increasing normal pigmentation and repigmenting vitiliginous skin are discussed. The fear that long-term psoralen and UV radiation treatment might induce skin tumors has not been realized in practice. (14 refs.)

- 78-0073 Viral Etiology of Human Tumors.** (Ger) Bauer, H. (Giessen, W. Germany). *Geburtshilfe Frauenheilkd* 37: 975-976; 1977.

Whether or not there is a viral etiology for human tumors is still unclear. Recent research is being focused on herpes viruses, adenoviruses, papilloma viruses, and oncornaviruses. (no refs.)

- 78-0074 Molecular Biology of Tumor Viruses.** (Ger) Sauer, G. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, D-6900 Heidelberg, W. Germany). *Naturwissenschaften* 64(10): 518-524; 1977.



Tumor virus genomes become integral parts of the host cell's genetic material (DNA), and many biological functions, such as oncogenicity, have been assigned to specific regions of the virus DNA. Transformation may depend not only on the oncogenic region of the viral genome but also on the site of integration in the host cell DNA. (52 refs.)

78-0075 **Virus and Cancer.** (Dut) Hageman, P. (Amsterdam, Netherlands). *Ned Tijdschr Geneesk* 121(38): 1470-1471; 1977.

No definite relationship has as yet been established between virus and cancer. There has been no evidence of virus in many tumors induced by chemicals or radiation, and tumor viruses do not appear to cause transformation in all cases. (8 refs.)

78-0076 **Herpes Simplex Virus (HSV-1 and HSV-2) Infection: Clinical and Oncogenic Properties.** (Ger) Dostal, V. (Institut für Krebsforschung, Universität Wien, Borschkegasse 8a, A-1090 Vienna, Austria); Fanta, D.; Reiss-Gutfreund, R. J. *Wien Klin Wochenschr* 89(22): 741-748; 1977.

The oncogenic potential of herpes simplex virus types 1 and 2 is reviewed along with the epidemiology, clinical features, and immunological reactions of the diseases caused by these viruses. Particular attention is focused on recent data dealing with mechanism of primary and chronic type 1 infections. (62 refs.)

78-0077 **Herpesvirus Homnis Type 2 in Women and Newborns.** (Eng) Bahr, J. E. (Wichita State Univ. Dept. Nursing, Wichita, KS). *Matern Child Nurs* 3(1): 16-21; 1978.

The dangers of herpesvirus infections in newborns of infected mothers is outlined. Herpesvirus hominis type 2 is a self-limiting venereal disease in the adult, but the respective rates of cervical dysplasia and in situ carcinoma in women with this infection are > 2 and > 8 times those in uninfected women. Mental retardation, microcephaly, intracranial calcifications, microphthalmia, retinal dysplasia, and chorioretinitis have been attributed to intrauterine herpesvirus infection. (26 refs.)

78-0078 **Infection by RNA Tumour Viruses.** (Eng) Bose, S. K. (Dept. Microbiology, St. Louis Univ. Sch. Medicine, St. Louis, MO 63104). *J Sci Ind Res* 36(3): 135-145; 1977.

A review is presented of several unique features of RNA tumor virus interaction with the host. In general, sarcoma viruses are defective in their ability to replicate. Since all preparations of infectious sarcoma viruses contain a sizable proportion of leukemia virus, and since the virions released by clonal isolates of murine sarcoma virus-infected cells have either a restricted host range or are non-infectious and have 0 to 25% reverse transcriptase activity, apparently the bulk of the viral reverse transcriptase in a given preparation is leukemic. RNA viral infections also have a requirement for DNA synthesis early after infection. Evidence has indicated that both extrachromosomal and chromosomal DNA syntheses are involved in the establishment of infection by murine sarcoma virus and that secondary rounds of infection by progeny play a minor role in the establishment of a max rate of virus synthesis. All infectious RNA viruses contain reverse transcriptase activity. Data have indicated that not only is viral DNA present in cells infected with virus, expressing helper activity, or group specific antigen, but also that the extent of transcription may be limited in many cases. All cells have nucleotide sequences in their chromosomal DNA which can code for tumor virus RNA; regulatory genes control the expression of the viral genes. The current model of virus infection is discussed. (137 refs.)

78-0079 **Purification of Oncornaviruses by Concanavalin A.** (Eng) Stewart, M. L. (Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Building 6, Room 140, NIH, Bethesda, MD 20014). In: *Concanavalin A as a Tool*. Bittiger, H.; Schnebli, H. P., eds. (New York: John Wiley & Sons): 639 pp., 479-501; 1976.

A technique that uses concanavalin A (ConA) to purify Friend leukemia virus from infected 3T3 mouse fibroblasts is presented. After the medium is centrifuged to remove cells and debris, 800 µg/ml Con A are added to agglutinate the virus. The agglutinated particles are then solubilized and fractionated. The morphological appearance of the virus, and its infectivity appear to be unaffected by the procedure. The optimization of this technique for the purification of other viruses is described. Electrophoresis of the purified virus can be used to determine the viral structural components. (31 refs.)

78-0080 **Selection of Concanavalin A-resistant Variants of Virus-transformed Cells.** (Eng) Culp, L. A. (Dept. Microbiology, Case Western Reserve Univ., Cleveland, OH 44106). In: *Concanavalin A as a Tool*. Bittiger, H.; Schnebli, H. P., eds. (New York: John Wiley & Sons): 639 pp.; 623-634; 1976.



Concanavalin A (Con A) can be used to isolate revertant variants of virus-transformed cells in complete or serum-free medium. With complete medium, Con A is added and, 48 hr later, the agglutinated cells are removed; the revertant cells can then be grown in fresh medium. In serum-free medium, cells attached to substrates are washed free of medium and Con A is added. After about 3 hr, the remaining substrate-adherent cells can be washed with buffer and regrown as colonies in complete medium. The frequency of Con A revertant cells in populations of virus 40 (SV40)-transformed cells is approx 1 in  $10^5$  transformed cells. These revertants have a large, flat morphology, allow rescue of infectious virus, have a high sialic acid composition and high collagen content in confluent cultures, are hypertetraploid, deposit a high proportion of protein and polysaccharide on the substrate, are unaffected by substrate-attached material, and have large quantities of highly ordered arrays at points of cell contact with cells and substrate. Revertants may arise by abnormal cytokinesis during mitosis or by fusion of a transformed cell. It is not known if the viral DNA remains integrated into host DNA or if it exists as an episome. Resistance to Con A agglutinability may result from immobility of the lectin receptor sites and/or reduced concentrations of these sites per area of cell membrane. (25 refs.)

- 78-0081 **Neoplasia, Autoimmunity and the Immune Response.** (Eng) Roubinian, J. R. (Dept. Immunology and Arthritis, Univ. California, San Francisco, CA); Talal, N. *Adv Intern Med* 23: 435-450; 1978.

In this review article, particular attention is focused on immunologic regulation in terms of lymphocyte heterogeneity, macrophages, immune-response genes, suppressor T cells, defense mechanisms against neoplasia, the autoimmunity and lymphoid neoplasia, cell membrane organization, and a model of how plasma membrane alterations may lead to neoplasia. (69 refs.)

- 78-0082 **Immunosuppression and Metastasis.** (Eng) Stjernsward, J. (Ludwig Inst. Cancer Res., Lausanne Branch, Lausanne, Switzerland); Douglas, P. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 319-331; 1977.

In this review article, the question of whether the facilitation of metastasis by immunosuppression found in experimental animals is relevant to the human situation is explored. Results showing that nidation and/or local outgrowth of tumor cells may be facilitated in irradiated human tissues are documented. Over the last 20 yr > 4,000 patients were investigated in clinically controlled trials in which the main difference

was whether or not the patient received postoperative radiotherapy. There is concordance between these data and the experimental animal data, which show increased disseminated disease after irradiation, probably as a result of radiation-induced immunosuppression. Experience with human breast and ovarian cancer indicates that prophylactic irradiation of the tumor bed after complete removal of the primary may be harmful when there is a high frequency of occult disseminated disease outside the irradiated area. Illustrations of an outgrowth of tumor cells that was limited exactly to the field of irradiation are included. In rare circumstances, not yet understood, tissue damage after irradiation may facilitate nidation and/or local outgrowth of metastases. (52 refs.)

- 78-0083 **Humoral Immune Factors in Metastasis in Human Cancer.** (Eng) Lewis, M. G. (McGill Univ. Cancer Res. Unit, Montreal, Quebec H3G 1Y6, Canada); Phillips, T. M.; Rowden, G.; Jerry, L. M. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 245-258; 1977.

The role of humoral immunity is reviewed in relation to two modes of metastatic spread in human tumors, blood-borne and via regional lymph nodes. Antitumor antibodies may have a positive role in the control of blood-borne metastasis. Antibody reacting with the surface of tumor cells in the absence of complement can prevent the adherence of these cells, but it cannot produce lysis. The presence of complement, however, may result in both nonadherence and subsequent lysis. Some degree of relationship has been demonstrated between the stage of disease and the presence of some form of humoral immunity. The antimembrane antibody (individually specific) appears to be the form most clearly related to disease stage in that it is largely confined to the early premetastatic phase of malignant melanoma. The antibody to cytoplasmic or internal antigens (group-specific) varies independently of disease stage and often persists into the metastatic phase. Germinal center hyperplasia and the B-cell content of the lymph nodes increase with progressive involvement of the nodes by tumor cells. The increase in B-cell activity may be largely due to the production of antibody against any membrane antigen in the same nodes. Antibodies against several different components of the IgG molecule have been detected in the sera of cancer patients. It is hypothesized that some form of immune derangement occurs in patients with malignancy, resulting in anergy, anti-antibodies, and immune complexes. (59 refs.)

- 78-0084 **Innate Host Resistance to Malignant Cells Not Involving Specific Immunity.** (Eng) Alexander, P. (Div. Tumour Immunology, Chester Beatty Res. Inst., Belmont, Sutton, Surrey, England). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.;



Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 259-275; 1977.

Experimental observations on the role of immunity in both the genesis and subsequent biological behavior of malignant tumors are interpreted on the basis of specific and nonspecific T-lymphocyte responses. The first line of defense against a malignant cell is the mononuclear phagocyte, which has the capacity to recognize surface properties characteristic of malignant transformation. Almost nothing is known, however, about either the cytotoxic mechanisms by which a suitably activated macrophage kills tumor cells or the surface characteristic that allows macrophages to distinguish between normal and malignant cells. Nonspecific immunity directed against tumor cells may also be mediated by lymphocytes. Available data suggest that cells involved in nonspecific (or innate) immunity control incipient neoplastic cells that arise sporadically. Large masses of tumors or tumors released into the circulation as clusters or conglomerates of tumor cells, which remain after radio- or chemotherapy, are relatively invulnerable to the innate mechanisms of immunity and require processes of specific immunity if they are to be controlled. Metastatic spread and curability by chemo- or radiotherapy are determined, therefore, in part by the magnitude of the specific host response. (52 refs.)

**78-0085 Discussion Summary: Immunologic Aspects and Tumor Immunity.** (Eng) Lewis, M. G. (Cancer Unit, McGill Univ., Montreal, Quebec, Canada). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Meyers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 353-355; 1977.

Host-tumor interactions in experimental carcinogenesis are reviewed. The topics covered include the role of macrophages in combatting metastatic spread, radiation-induced enhancement of lung metastases, metastatic spread in hemopoietic neoplasms, and the different patterns of metastasis observed in virus- and chemical-induced lymphomas. The use of dogs as a model for studying human metastases is suggested. (no refs.)

**78-0086 The Immunoregulatory Role of Cholesterol and Other Lipids: A Hypothesis.** (Eng) Roman-Franco, A. A. (Dept. Pathology, Univ. Puerto Rico Sch. Medicine. G.P.O. Box 5067, San Juan, Puerto Rico 00936); Santiago-Delphin, E. A. *Med Hypothesis* 3(6): 235-240; 1977.

An inverse correlation exists between cholesterol concentration and membrane fluidity and between cholesterol concentration and membrane permeability. Since diets rich in fatty

acids reduce immunological responsiveness, it is proposed that the dietary effect on fluidity alters the immune response. Increasing concentrations of cholesterol or other unsaturated fatty acids would then favor a tolerogenic signal from an antigen. Since spontaneously arising signals are weakly antigenic or nonantigenic to the host, the cholesterol-induced alterations in the antibody membrane would permit the tolerogenic signal to be received. Thus, hypercholesterolemic patients will have a diminished immune responsiveness to moderately strong antigens and a little or no response to weak antigens. Prolonged maintenance of this state will lead to a higher incidence of neoplasms in these patients than in normal subjects. The fact that diets rich in cholesterol or unsaturated fatty acids have been associated with cancer of the colon and breast lends support to this hypothesis. (71 refs.)

**78-0087 Bone Sarcomas: Etiology and Immunology.** (Eng) Sinkovics, J. G. (section Clinical Tumor Virology and Immunology, Dept. Medicine, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Thota, H.; Romero, J. J.; Waldinger, R. *Can J Surg* 20(6): 494-503; 1977.

Although the etiology of bone sarcomas is unknown, radiation is the best-documented physical factor in sarcomagenesis. Trauma, host factors such as von Recklinghausen's disease, and oncornaviruses have also been implicated. Patients with skeletal sarcoma respond immunologically to autologous and allogeneic sarcoma cells; immunotherapy may increase a patient's immune reaction, but no substantial benefits have been obtained. (72 refs.)

**78-0088 Factors Influencing Development of Bone Metastases.** (Eng) Powles, T. J. (Dept. Medicine, Royal Marsden Hosp., Surrey, England); Easty, G. C.; Easty, D. M.; Neville, A. M.; Dowsett, M. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 425-429; 1977.

Factors that may influence the development of bone metastases are discussed. Breast tumors (which preferentially metastasize to bone), when cultured in vitro, possess a marked ability to break down bone in organ culture. These tumors are able to synthesize prostaglandins as well as other osteolytic factors. This in vitro osteolysis can, in part, be inhibited by prostaglandin-synthesis inhibitors such as aspirin or indomethacin. Only patients whose tumors possess in vitro osteolytic activity have or develop bone metastases, suggesting that development of tumor metastases in bone may depend on the ability of tumors to release substances that break down bone. In animal experiments, early osteolytic develop-



ment depended on osteoclast activity presumably stimulated by something released by the tumor cells. Prostaglandin synthesis by host inflammatory cells may also be an important factor in the host defense against metastatic development. Use of prostaglandin-synthesis inhibitors such as aspirin may, therefore, enhance metastatic growth in tissues where the antiosteolytic effect is not important. It is concluded that the spread and behavior of tumors in bone may depend on the biochemical and biological properties of tumor cells, particularly the production of biologically active agents such as prostaglandins. (2 refs.)

- 78-0089 The Cell Surface and Metastases.** (Eng) Poste, G. (Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 19-47; 1977.

This review article begins with a discussion of the experimental approaches and problems in analyzing the surface properties of malignant cells. Cell-surface changes associated with the neoplastic transformation of cells cultured in vitro are tabulated, along with selected review articles. Identification of the mechanisms involved in controlling the different mobilities of the membrane components, notably the integral proteins and glycoproteins, is important for understanding the altered surface properties displayed by tumor cells, since evidence indicates that the intramembrane mobility of these components may be increased in neoplastic cells. There is a functional relation between the topography and dynamics of surface macromolecules and the control of cell-surface properties. The question of whether perturbation of the transmembrane control mechanisms regulating the mobility and distribution of surface component might be responsible for certain altered surface properties exhibited by tumor cells is discussed in detail. Each step in metastasis formation, ie, the sequential release of cells from the primary tumor, their dissemination to distant sites, and their arrest, survival, and proliferation in these new locations, is surveyed in light of current data. (118 refs.)

- 78-0090 Cell Surfaces and Blood-borne Tumor Metastasis.** (Eng) Nicolson, G. L. (Dept. Developmental and Cell Biology, Univ. California, Irvine, CA 92717). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 163-174; 1977.

Studies of factors that may influence the differing metastatic potentials of various B16 melanoma cells in C57BL/6 mice are reviewed. Experiments on the organ selectivity of blood-borne metastatic variant lines of B16 indicated that cells selected for increased lung metastasis may possess unique properties that determine their distribution and subsequent survival and growth independent of route of entry into the circulation. Tumor cell lines that metastasized preferentially to the lung could be retargeted to the brain using in vivo selection technique. The tumor line seemed to form colonies almost exclusively in the ventricle brain regions, suggesting not only organ preference but also regional preference within that organ. These results suggest that further selection could lead to a tumor cell line that will form only brain colonies and, perhaps, only brain colonies in specific brain regions. Enzymatic differences between the B16 melanoma lines of differing metastatic potentials were not detected in vitro, but they may be important in local tumor invasion. The homotypic or heterotypic rates of adhesion (B16 to B16 or other cells) that could be important during blood-borne transport were examined by in vitro assays. The results indicate that modifications in adhesive behavior accompany selection of highly metastatic variants. These modifications may aid in blood-borne tumor arrest and trapping of multicell emboli that form in the circulation. (68 refs.)

- 78-0091 Hemostasis and Experimental Cancer Dissemination.** (Eng) Donati, M. B. (Lab. Hemostasis and Thrombosis Res., Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy); Poggi, A.; Mussoni, L.; de Gaetano, G.; Garattini, S. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 151-160; 1977.

Cancer cell dissemination and implantation in distant organs appear to be influenced by several hemostatic factors. Activation of fibrinolysis and/or other proteolytic activities associated with malignant cells may contribute to cohesive failure in solid tumors, resulting in release of cancer cells into the bloodstream and lymph. Platelet aggregates and tumor procoagulant activities may facilitate the arrest of tumor cell clusters in the microcirculation. Endothelial damage and changes in vascular permeability may be provoked by platelet aggregates or substances derived from platelets or the coagulation/fibrinolysis system. Hemostatic changes during cancer dissemination have been studied in the Lewis lung carcinoma (3LL) model. These changes were markedly different during the metastatic growth of 3LL in three experimental systems, spontaneous metastasis with and without removal of the primary tumor and bloodborne tumor emboli. Only when the primary was present were thrombocytopenia, anemia, and hyperfibrinogenemia observed. A coumarin anticoagulant, racemic sodium warfarin, reduced the number and wt of



spontaneous lung metastases in 3LL-bearing mice. Lung metastases were increased in mice kept defibrinated during the entire period of tumor development by batroxobin, a substance extracted from snake venom. However, when mice were defibrinated only during metastatic growth, with or without removal of the primary, the metastases were slightly decreased. This suggests that fibrin may play different roles in the various phases of metastatic spread of the same tumor. (63 refs.)

- 78-0092 Paradoxical Position of Vertebral Veins in Cancer Carriage.** (Eng) Onuigbo, W. I. (Dept. Pathology, General Hosp., Enugu, Nigeria). *Med Hypotheses* 3(6): 267-269; 1977.

In 1940, O.V. Batson postulated that the interconnections in the vertebral venous system, which responds to almost all trunk movements, including coughing, would facilitate cancer metastases. However, a review of 6,000 cases of lung cancer, in which coughing is a prominent feature, revealed that about 33% had no invasion of organs supplied by these veins and only 1 had invasion of all of them. Since no barriers exist between the halves of the body, it was also suggested that metastases across the midline would be common. This is rarely observed in lung cancers. In addition, since lymph nodes are disseminated throughout the venous system, diffusion of cancers through them should be random. However, the pattern of spread shows an orderly distribution: deposits tend to be wholly on one side, show asymmetry, or diminish in size in centrifugal order. It is suggested that in most metastases, lung cancer cells form colonies and then utilize the means of spread that are open to them in a manner contradicting Batson's theory. The vertebral venous system, in terms of cancer dissemination from the lung to other organs, the opposite lung, and lymph nodes, occupies a paradoxical position. (20 refs.)

- 78-0093 Comments Regarding the Distribution and Fate of Circulating Tumor Cells.** (Eng) Proctor, J. W. (Div. Radiation Oncology, Clinical Radiation Therapy Res. Center, Allegheny General Hosp., Pittsburgh, PA 15212). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 493-496; 1977.

The question of whether the death of blood-borne tumor cells is due to active destruction or passive deterioration is discussed, together with nonimmune factors that determine secondary and tertiary spread patterns. Effective chemotherapy depends on the recognition that the distribution and growth patterns of metastases are likely to vary from one cancer to another, as they do from one animal model to another. (14 refs.)

- 78-0094 Discussion Summary: Establishment and Distribution of Metastasis.** (Eng) Lewis, M. G. (Cancer Unit, McGill Univ., Montreal, Quebec, Canada). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 241-243; 1977.

The various presentations on cancer invasion and metastasis are summarized. One of the most important factors is the adherence of tumor cells to the endothelium of blood vessels. The ability of tumor cells from different tumor types to become arrested in different organs after iv injection might be affected by immunological factors. Considerable discussion centered on the problems of identifying the distribution of tumor cells, particularly using labeled cells with detachment of the label, and the subsequent recirculation or further spread of tumors lodged in certain organ sites. Biochemical criteria that might be important in metastasis were reviewed with the conclusion that although numerous serum factors, metabolic products, and ectopic hormones have been studied, few studies give enough reliable information of any great importance. The inhibitory effect of the primary on metastatic spread was examined with the conclusion that nutritional, blood supply, immunological, and humoral metastatic inhibitor effects may all be relevant. This phenomenon, however, is not a uniform nor a reproducible one, since the opposite effect is seen in some tumor systems. The different types of tumor vessel and fibrin interplay, plus the many other factors considered, both in the coagulation and immune systems, may alter or modify the speed with which tumor cells become established metastases. (no refs.)

- 78-0095 Cell Proliferation, Differentiation, and Migration in the Gastric Mucosa: A Study on the Background of Carcinogenesis.** (Eng) Fujita, S. (Dept. Pathology, Kyoto Prefectural Univ. Medicine, Kyoto, Japan); Hattori, T. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 21-36; 1977.

Human and golden hamster gastric mucosa was examined to study the role of cell proliferation, differentiation, and migration in carcinogenesis. The subclinical growth of early cancer in humans is estimated to be 16-24 yr. However, few cells survive more than a few months. In normal mucosa, there is little space for cancer cells to hide and develop for several years without their being sloughed off, as are the rest of the cells. One possible exception would be undifferentiated cancer. These cells are not tightly bound to neighboring cells, and they can migrate into the glandular portion of the fundic gland and remain there for long periods or they can penetrate directly into the lamina propria and avoid the sloughing-off



mechanism. In intestinal metaplasia, however, there is progressive obliteration and embedding of glandular elements deep in the lamina propria or muscularis mucosa. With obliteration of the glandular branches in advanced stages, these segments could become isolated and serve as nests for the developing carcinoma. Isolation and embedding of glandular elements also occur in adenomas. Intestinal cancers can arise by the same mechanism, since cell turnover in the intestine is also too rapid to allow cells to survive for long. (15 refs.)

- 78-0096 The Stability of Events in the Natural History of Neoplasia.** (Eng) Pitot, H. C. (Dept. Oncology, McArdle Lab. Cancer Res., Medical Sch., Univ. Wisconsin, Madison, WI 53706). *Am J Pathol* 89(3): 703-716; 1977.

Previous studies of the natural history of neoplasia, using mouse skin as a model, demonstrated that epidermal carcinogenesis involves at least two different phases. The first of these, termed initiation is essentially irreversible; the second phase, that of promotion, may be modulated or reversed by a variety of environmental conditions. More recently, similar stages have been demonstrated for other organ systems during carcinogenesis, murine liver in particular. However, investigations in a variety of systems, including plants, amphibians, and mammals, indicate that the initiation process may not always be irreversible; in plants and in murine teratomas, the neoplastic process appears to be reversible from its initial stages under appropriate conditions. A proposed scheme is presented that takes into account the reversibility of the initiation process in the development of neoplasia. (50 refs.)

- 78-0097 Calcium and Cancer.** (Eng) Miller, K. (Aker Sykehus, Oslo 5, Norway). *Med Hypothesis* 3(6): 263-264; 1977.

A review of the literature dealing with the role of Ca in cancer indicates that malignant cells consistently have a lower Ca:K ratio than normal cells. Furthermore, the lack of adhesiveness of neoplastic cells shows a positive covariation with reduced Ca content. This reduction is most probably due to an alteration of the membrane complexes that bind calcium. The electrostatic repulsion that occurs between the surfaces of cancer cells could be the result of this inability to bind Ca ions. It is suggested that following malignant transformation, there is an alteration in the cellular membrane that brings about a reduction in Ca content. This in turn increases membrane permeability (brings about rapid growth), promotes the leakage of proteolytic enzymes, and increases the net negative surface charge, all of which facilitate invasion and metastasis. (17 refs.)

- 78-0098 Discussion Summary: The Process of Metastatic Spread.** (Eng) Alexander, P. (Div. Tumor Immunology, Chester Beatty Res. Inst., Belmont, Sutton, Surrey, England). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 161-162; 1977.

Possible links between tumor angiogenesis factor production and tumor dormancy and between plasminogen activator production and tumor invasion are discussed. (no refs.)

- 78-0099 Biochemical Criteria of Metastatic Growth in Human Cancer.** (Eng) Bodansky, O. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 199-211; 1977.

Several biochemical parameters that may serve as aids in following the growth or regression of metastases in cancer patients are considered. Elevated serum alkaline phosphatase activity is indicative of metastatic disease involving the skeletal and hepatobiliary systems. Serum 5'-nucleotidase activity is elevated in hepatobiliary disease but not in skeletal disorders. Levels of human chorionic gonadotropin (HCG) and various polyamines (putrescine, spermine, and spermidine) are elevated in the serum and urine of patients with several types of cancer. Three case histories illustrate the relationship between changes in biochemical parameters and the course of metastatic disease. One case demonstrates the correlation between elevation of serum phosphohexose isomerase and clinical and other biochemical manifestations of metastases in the skeleton and/or liver. Another illustrates the parallelism between serum glycoprotein concentration and the institution of various therapeutic measures, namely, surgery, cobalt radiation, and nitrogen mustard, in a patient with lung carcinoma plus metastatic disease. The third case shows some parallelism among therapy, clinical condition, and carcinoembryonic antigen (CEA) levels in metastasis following breast cancer, but the sequential determinations of CEA levels and the accompanying clinical observations were not done at sufficiently close intervals. Several preliminary studies have appeared on the relationship between clinical status and sequential determinations of human chorionic gonadotropin, human placental lactogen, and  $\alpha$ -fetoprotein, but more detailed studies are needed. (35 refs.)

- 78-0100 Inhibitory Effect of a Primary Tumor on Metastasis.** (Eng) Sugarbaker, E. V. (Dept. Surgery, Div. Oncology, Univ. Miami Sch. Medicine, Miami, FL 33152); Thornthwaite, J.; Ketcham, A. S. In: *Cancer Invasion*



and Metastasis: *Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 227-240; 1977.

Experimental evidence related to the inhibitory effect of a primary tumor on metastases, on other implanted tumors, or on itself is examined, and possible mechanisms for this type of inhibition are reviewed. In spontaneously metastasizing murine tumor systems, the growth rate of established pulmonary metastases accelerated after surgical resection of the primary tumor. Similar results have been obtained in both hamsters and rats, the common observation being that the growth rate of disseminated tumor cells is stimulated by the surgical removal or irradiation ablation of the primary. The inhibitory influence of a primary tumor on the growth of metastasis may be one manifestation of a more generalized phenomenon; ie, an inhibitory influence of an expanding tumor mass on itself. Other manifestations of this phenomenon include the inhibitory influence of: (1) one tumor mass on a second tumor implant, (2) early-appearing metastases on primary tumor growth, (3) a primary tumor on itself, and (4) an ascites cell or tissue culture population on further growth. The phenomenon, therefore, seems to be a negative feedback mechanism in otherwise uncontrolled tumor growth. The intensity of this negative feedback mechanism increases with expanding tumor mass. Mechanisms for tumor inhibition may include nonspecific systemic mitotic inhibitors, tumor chalones, and polyamines metabolism. (29 refs.)

**78-0101 Overview of the Biology and Pathology of Metastasis.** (Eng) Davies, J. N. (Albany Medical Coll., Albany, NY 12208). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 13-18; 1977.

In most cases, metastases will duplicate the morphological and functional features of the primary growth. With the exception of the two major routes of dissemination (the lymphatics and the veins), all other aspects of metastases are unpredictable. These problems are summarized, along with factors that should be considered in animal studies of metastatic spread. (3 refs.)

**78-0102 Increasing Female Mortality from Lung Cancer.** (Eng) Anonymous (No affiliation given). *Med J Aust* 2(8): 235-236; 1977.

Based on World Health Organization statistics, female deaths from lung cancer increased sharply between 1965-1969 and

1970-1972. The increase was 39% for the US, 31% for Denmark, 24% for Sweden, 19% for Finland, England, and Wales, 17% for the Netherlands, and 16% for Japan and Poland. (1 ref.)

**78-0103 Present Status of Adenomatosis Coli in Japan.** (Eng) Utsunomiya, J. (Second Dept. Surgery, Tokyo Medical and Dental Univ., Tokyo, Japan). In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 305-321; 1977.

Data of the adenomatosis coli (AC) tumor registry in Japan are reviewed. AC is inherited as a Mendelian dominant disease that inevitably terminates in colon malignancy. In this registry, AC includes Gardner's syndrome but excludes Peutz-Jeghers' syndrome. The incidence of familial cases from 38% in 1958 to 58.5% in 1975. The age-specific incidence of large bowel cancer in AC patients demonstrates a shift toward the younger age groups. According to the multi-hit theory of carcinogenesis, the AC group would have received the initial hit(s) in the prezygotic stage of development, requiring fewer postzygotic hits to develop cancer than the general population. Extracolonic lesions in AC patients, including Gardner's syndrome, occult osteomatous changes in the mandible, gastric lesions, and duodenal polyps are discussed. Fibroblasts of AC patients have specific clonal morphology and growth characteristics, are highly susceptible to mitomycin C, and are more resistant to killing by <sup>60</sup>Co than normal cells, and they incorporate <sup>3</sup>H-thymidine not only into the adenoma but also into the nonadenomatous mucosa of the patients. (20 refs.)

**78-0104 The Identification of Individuals at High Risk for Large Bowel Cancer. An Overview.** (Eng) Lipkin, M. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021). *Cancer* 40(5, Suppl): 2523-2530; 1977.

Various inherited conditions that predispose an individual to the development of colonic cancer are reviewed. Early stages of abnormal growth of colonic epithelial cells and related factors plus environmental factors are discussed. Identification of early findings can be used to develop programs to prevent malignancy in high risk individuals. (68 refs.)

**78-0105 Colon Cancer: Etiological Issues and Prospects for Early Detection.** (Eng) Jaco, D. (Communi-



ty Health Education, Dept. Family and Community Medicine, Univ. Missouri-Columbia, Columbia, MO 65201). *Prev Med* 6(4): 535-544; 1977.

Studies of nutritional imbalances and deficits hold the most promise for detecting an etiological agent in colon cancer. The exact role of dietary fiber and animal fat in the disease is unknown. Public awareness of the seriousness of colon cancer and cooperation of public health officials can increase early detection, when the chances of long-term survival are good. (28 refs.)

- 78-0106 **Spontaneous Colon Cancer in Rats.** (Eng) Miyamoto, M. (Dept. Pathology, Osaka Univ. Medical Sch., Osaka, Japan); Takizawa, S. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 297-304; 1977.

A high incidence of spontaneous colon cancer was found in Wistar-Furth (WF) rats maintained through 15-18 generations by brother X sister mating. All rats were maintained on NMF breeding chow and received water ad libitum. There were 19 males and 12 females with tumors indicating a lack of sex preference. Each tumor was found in the ascending colon and, histologically, almost all were well-differentiated tubular adenocarcinomas. Although the total incidence could not be determined because some of the rats died before weaning, the establishment of family trees suggested involvement of an autosomal dominant or an autosomal recessive trait. A similar discrepancy developed when one study showed that a genetic disorder may play some part while another found the contrary to be the case. Thus, although tumor occurrence may be familial, factors other than genetic ones may be involved. (18 refs.)

- 78-0107 **Primary Liver Cancer in Adults.** (Fre) Ezraty, A. (Service d'hépatogastro-entérologie, hôpital Sainte-Marguerite, 270, boulevard de Sainte-Marguerite, 13274 Marseille Cedex 2, France); Gauthier, A. P. *Rev Prat* 27(50): 3409-3411; 1977.

Adult liver cancers are reviewed from the aspects of etiology, histology, diagnosis, and treatment. Compared to the incidence in Asians (10%-40% of all cancers) and in black Africans (as high as 90%), in whom the disease occurs in younger age groups and may be related to viral or parasitic diseases, the incidence of liver cancer in Europe, the US, and Australia is low. It is only 1%-3% of all cancers, and it appears in older subjects ( $\leq 60$  yr) with alcoholic cirrhosis or persons who had been exposed to certain chemicals. Painful hepatomegaly is

the presenting symptom in 33% of European patients and 70% of black Africans. Increased hepatic alkaline phosphatase and 5-nucleotidase levels and  $\alpha$ -fetoprotein levels  $\leq$  nanograms/ml are indicative of disturbed liver function. Noninvasive diagnostic techniques such as scintigraphy, ultrasonography, and tomography are valuable, but laparoscopy with puncture biopsy and arteriography actually establish diagnosis. (no refs.)

- 78-0108 **Hepatology in 1977.** (Fre) Etienne, J. P. (Service d'hépatologie et de gastro-entérologie, hôpital Antoine Beclère, 157, rue de la Porte-de-Trivaux, F 92141, Clamart, France); Buffet, C.; Chaput, J. C.; Labayle, D. *Rev Prat (Paris)* 27(53): 3605-3624; 1977.

In this review of drugs and other agents responsible for liver damage and disease, those that cause liver tumors are included. Although androgens, estrogens, and progesterone induce liver tumors in rats, few cases of hepatic carcinomas related to prolonged treatment with these hormones have been reported in humans. On the basis of numerous published studies since 1973, oral contraceptives have been shown to induce benign liver tumors such as adenomas and focal nodular hyperplasia. Polyvinyl chloride, arsenic, and thorotrast cause angiosarcomas of the liver. The carcinogenicity of polyvinyl chloride has recently been proved experimentally in the rat. (81 refs.)

- 78-0109 **Evolution and Diagnosis of Precanceroses.** (Ger) Hundeiker, M. (Zentrum für Dermatologie, Andrologie und Venerologie, Klinikum der Justus-Liebig-Universität, Gaffkystrasse 14, 6300 Essen, W. Germany). *Z Hautkr* 52(23): 1181-1199; 1977.

Precanceroses are transitory changes that occur during carcinogenesis. The morphological, diagnostic, and etiological aspects of several precanceroses, ie, solar and radiogenic keratoses, tar and oil keratoses, precancerous lesions induced by arsenic, Bowen's dermatosis, and leukoplakia, are reviewed. (40 refs.)

- 78-0110 **Chimeric Mice Derived from Normal Embryos Injected with Teratocarcinoma Cells.** (Eng) McBurney, M. W. (Dept. Biology, Univ. Ottawa, Ottawa, Ontario, Canada K1N 6N5). *Am J Pathol* 89(3): 685-686; 1977.

When injected into normal mouse embryos, embryonal carcinoma cells can behave like normal, nonmalignant cells and differentiate accordingly. In addition, the progeny of the in-



jected cells are capable of forming all tissues normally found in adult mice, including liver, hematopoietic, and lymphoid tissues. Embryonal carcinoma cells containing appropriate mutations could provide a mouse model for the study of human genetic diseases. (7 refs.)

- 78-0111 Epidemiological Aspects of Melanoma: A Review.** (Eng) McGovern, V. J. (Fairfax Inst. Pathology, Royal Prince Alfred Hosp., Camperdown, New South Wales 2050, Australia). *Pathology* 9(3): 233-241; 1977.

Epidemiological aspects dealing with the incidence of melanoma are reviewed. The primary factors are racial susceptibility, skin pigmentation, and latitude of domicile. Celts, Norwegians, and Swedes have a higher incidence of melanoma than people with a similar skin color living at the same latitudes. Melanoma, although rare in dark-skinned races occurs in a higher incidence in less pigmented regions, principally the sole of the foot and various squamous mucosae. A direct relationship exists between latitude, duration of residence in that latitude, and the incidence of melanoma; the incidence of melanoma is higher closer to the equator. Although there is a preponderance of females in areas of high incidence, they have a better survival rate than males. Pregnancy has no effect on the death rate from melanoma. Familial melanoma occurs at a younger age than normal in susceptible individuals and it has a random site distribution. Familial cases have a multiplicity of primary growths; hair, eye, and skin color have no effect on its occurrence. The relationship between nevi and melanoma is reviewed. Since 7% to 8% of all melanoma metastases have no demonstrable primary, an immunological role is implicated. However, no regression's have been identified in the internal viscera. (56 refs.)

- 78-0112 The Future Risk of Malignant Melanoma (Meeting Abstract).** (Eng) Lee, J. A. (Univ. Washington, Seattle, WA); Stock, R. W. *Yale J Biol Med* 50(5): 70; 1977. (no refs.)

- 78-0113 Human Pigmentation: Its Geographic and Racial Distribution and Biological Significance.** (Eng) Roberts, D. F. (Dept. Human Genetics, Univ. Newcastle upon Tyne, Newcastle upon Tyne, England). *J Soc Cosmet Chem* 28(6): 329-342; 1977.

Quantitative studies, based on reflectance spectrophotometry, have resulted in a better understanding of the genetics and biological significance of skin color variation. The genetic component of pigmentation variation is polygenic, and skin color is of moderately high heritability (60%-80%). The genetic basis of the differences between populations appears to reside in four gene pairs for the differences between Europeans and Africans and two gene pairs for the difference between Indians and Europeans. The close relationship between mean pigmentation and geographical variables, especially latitude, suggests that the biological role of melanin is to protect against UV radiation. Skin color is also involved in thermoregulation, vitamin D synthesis, and protection against infective and parasitic diseases. (33 refs.)

- 78-0114 Mass Surveys to Detect Cancer.** (Eng) Lawrence, E. (No affiliation given). *Nature* 270(5637): 464-465; 1977.

Cancer epidemiology in China focuses on mapping of cancer incidence and site, and comparing the incidence to that in domestic animals. These studies have indicated parallel high incidences of esophageal cancer in man and gullet cancer in chickens, and nasopharyngeal cancer in both man and pigs. Studies have indicated that the carcinogen must be something in the immediate environment of both man and the animals. Once the etiological agent is identified, efforts will focus on limiting exposure. (no refs.)

- 78-0115 A Proposal That Malignancies Represent Genetic Changes in Cell Surface RNA.** (Eng) Stuart, W. D. (Dept. Genetics, Univ. Melbourne, Parkville, Victoria, 3052, Australia). *Med Hypothesis* 3(6): 221-225; 1977.

It is proposed that exterior-organizer RNA (exoRNA) is involved in the assembly of permeases, lectin, receptor sites, transmembrane, microfilament attachment sites, hormone receptor complexes, and other membrane functions in normal cells. In malignant cells, however, either the exoRNA is not produced, is produced incorrectly, or is replaced by viral RNA from an inserted genome. Examples of the normal cell, the malignant cells with no exoRNA, the malignant cell with viral RNA, and the cell with mutant exoRNA, are presented. The hypothesis does not depend on the number of genes coding for exoRNA, although more than one are expected. Because of the similarity between malignant cells and rapidly dividing normal cells, such as those present in fetal tissue, it is suggested that exoRNA may also play a role in development. (27 refs.)



## CHEMICAL CARCINOGENESIS

- 78-0116 **Intrasanguine Host-mediated Assay with *Salmonella typhimurium*.** (Eng) Arni, P. (Res. Dept., Pharmaceuticals Div., CIBA-GEIGY Ltd., Basel, Switzerland); Mantel, T.; Deparade, E.; Muller, D. *Mutat Res* 45(3): 291-307; 1977.

*Salmonella typhimurium* LT-2 strains TA1535 and TA98 were intrasanguinely administered to male albino NMRI mice to test the mutagenicity of diethylnitrosamine, cyclophosphamide, ethyl methanesulfonate, thiotepa (N,N',N''-triethylenethiophosphoramidate), and dimethylaminoazobenzene. The mice were fasted for 12 hr, and the test substances were administered po, ip, or sc at 2 hr, 1 hr, and immediately before injection of the bacteria. The volume of the po and ip doses was 20 ml/kg. Immediately after the last injection of test substance, 0.2 ml of the bacterial suspension was injected into the lateral vein of the tail. Bacterial recovery rates from the liver 1 hr after administration ranged from 2.72% to 23.5%. All the known mutagens caused a measurable mutagenic effect. A comparison of these results with the literature indicated that the intrasanguine assay is more sensitive than the ip one and that TA1535 and TA98 are well-suited for this type of test. (40 refs.)

- 78-0117 **Bacterial Mutagenesis and Liver Activation in the Assessment of Carcinogens (Meeting Abstract).** (Eng) Schoeny, R. S. (Univ. Cincinnati, Cincinnati, OH). *Diss Abstr Int [B]* 38(5): 2036B-2037B; 1977. (no refs.)

- 78-0118 **Sampling Granular Foodstuffs for Aflatoxin.** (Eng) Whitaker, T. B. (U.S. Dept. Agriculture, Agricultural Res. Service, North Carolina State Univ., Raleigh, NC 27607). *Pure Appl Chem* 49(11): 1709-1717; 1977.

Methods for estimating aflatoxin contamination in granular foodstuffs are presented that afford max protection to the producer and consumer. A batch is accepted or rejected if the contamination level is below or above a given range. If the level is within the range, up to two more assays are made before the batch is accepted or rejected. Use of this procedure with the 1976 peanut harvest, which indicated its acceptability, is reported. (10 refs.)

- 78-0119 **Effect of Dietary Protein on the Response of Rainbow Trout (*Salmo gairdneri*) to Aflatoxin B<sub>1</sub>.** (Eng) Lee, D. J. (Agricultural Res. Center, Washington

State Univ., Pullman, WA 99163); Sinnhuber, R. O.; Wales, J. H.; Putnam, G. B. *J Natl Cancer Inst* 60(2): 317-320; 1978.

The effect of type and quantity of dietary protein on the susceptibility of rainbow trout (*Salmo gairdneri*) to the carcinogenicity of aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) was investigated. Four diets containing 49.5% or 32% casein or 49.5% or 32% fish protein concentrate (FPC) were prepared. Duplicate lots of 90 fish were fed either 0, 2, 6, 18, or 54 ppb AFB<sub>1</sub> incorporated into one of the above diets for 12 mo. A 30-fish sample was taken from each tank at 6, 9, and 12 mo, and liver and body wts were recorded and the livers preserved for histologic examination. Both levels of casein produced nearly identical incidences of hepatomas at each AFB<sub>1</sub> level. The high-FPC diet produced significantly more hepatomas at the two lower levels of AFB<sub>1</sub> than did any of the other diets, but the low-FPC diet reduced the incidence of hepatoma significantly at all AFB<sub>1</sub> levels. Liver size (percent body wt) was smaller at higher AFB<sub>1</sub> levels in all instances. The growth of fish given the low-casein diet was less than that of the other groups. Histologic examination of the hepatomas did not reveal any diet-related differences. The pathologic changes were the same as those described previously for AFB<sub>1</sub>-induced tumors in trout. (18 refs.)

- 78-0120 **Interrelationships of Dietary Protein Level, Aflatoxin B<sub>1</sub> Metabolism, and Hepatic Mitochondrial Epoxide Hydrase Activity.** (Eng) Adekunle, A. A. (Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria); Hayes, J. R.; Campbell, T. C. *Life Sci* 21(12): 1785-1792; 1977.

The effect of dietary protein level on hepatic epoxide hydrase and aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) metabolism was investigated in microsomal systems from male Sprague-Dawley-derived rats. The rats were divided into three groups: Group 1 was fed a 5% casein diet ad libitum, Group 2 a 20% casein diet pair-fed to Group 1, and Group 3 a 20% casein diet ad libitum. The 5% diet was kept isocaloric to the 20% casein diet by replacing casein with an equivalent amount of sucrose. Metabolism was determined in a flask containing 0.5 ml of a microsomal suspension equivalent to 0.5 g liver and 5  $\mu$ l of a dimethyl sulfoxide solution containing 10  $\mu$ g AFB<sub>1</sub>/ $\mu$ l. A comparison of microsomal protein and cytochrome P-450 levels in the three groups indicated that both were significantly decreased in the low-protein Group 1 animals; the livers of these animals were increased in wt and fatty in appearance. After 1 hr, Group 1 had 25  $\mu$ g AFB<sub>1</sub> remaining, Group 2 21.33  $\mu$ g, and Group 3 19.50  $\mu$ g. Group 2 had the highest concentration of the metabolites AFQ<sub>1</sub> and AFM<sub>1</sub> followed by Groups



3 and 1. AFB<sub>2</sub>a was not detected in any incubation mixture. Kinetic parameters for the hydration of styrene oxide by epoxide hydase indicated that Group 1 had an increase in *K<sub>m</sub>* but a decrease in *V<sub>max</sub>* and Groups 2 and 3 had a decrease in both parameters. Thus, epoxide hydase activity in low-protein animals may have a decreased ability to metabolize AFB<sub>2</sub> 2,3-epoxide if it responds in the same manner as styrene oxide. (42 refs.)

**78-0121 Mutagenicity and Inducibility of DNA Single-Strand Breaks and Chromosome Aberrations by Various Mycotoxins.** (Eng) Umeda, M. (Tissue Culture Lab., Yokohoma City Univ. Sch. Medicine, Urafune-cho 2-33, Minami-ku, Yokohama 232, Japan); Tsutsui, T.; Saito, M. *Gann* 68(5): 619-625; 1977.

The mutagenicity of nine mycotoxins and the efficiency of those found to be mutagenic in producing DNA single-strand breaks and chromosome aberrations were examined in FM3A cells, a C3H mouse mammary carcinoma cell line. Treatment of the cells with aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), mycophenolic acid (MPA), patulin (PAT), penicillic acid (PEA), and sterigmatocystin (STC) induced 8-azaguanine-resistant mutations, but treatment with chaetoglobosin B, fusarenone-x, (-)-luteoskyrin, and ochratoxin A did not. Of the five mutagens, AFB<sub>1</sub>, MPA, and STC had little effect on DNA single strands even at high concentrations (10, 32, and 3.2 µg/ml, respectively). Exposure to PAT and PEA produced severe breaks, but only at concentrations higher than those needed to induce mutations (10 and 32 µg/ml vs 0.32 µg/ml for PAT; 10 µg/ml vs 3.2 µg/ml for PEA). The incidence of chromosome aberrations correlated fairly well with mutagenicity for all five mutagens. Thus, the mutation/chromosome aberration assay is much more sensitive than DNA single-strand analysis in investigating the DNA-damaging effect of chemicals. (10 refs.)

**78-0122 Inhibition of Carcinogenic Effect of Bracken Fern (*Pteridium aquilinum*) by Various Chemicals.** (Eng) Pamukcu, A. M. (Div. Clinical Oncology, Dept. Human Oncology, Univ. Wisconsin Center Health Sciences, 1300 Univ. Ave., Madison, WI 53706); Yalciner, S.; Bryan, G. T. *Cancer [Suppl]* 40(5): 2450-2454; 1977.

The inhibitory effect of butylated hydroxyanisole (BHA), disulfiram, calcium chloride, and polyvinyl pyrrolidone (PVP) on the intestinal and urothelial carcinogenicity of bracken fern (BF) was determined in albino rats. The rats received a normal diet, a BF-containing diet (one-third of diet by wt), or either of these diets supplemented with one of the following: BHA (5 mg/g diet), disulfiram (5 mg/g diet), PVP (50 mg/g diet), or calcium chloride (20 mg/g diet). At 12 mo, the following results were noted: in the BF-treated group, 30/30 rats exhibited intestinal tumors and 22/30, urinary

bladder tumors. In the BF-BHA group, 15/20 rats showed intestinal tumors and 12/20, urinary bladder tumors. Of the 16 rats in the BF-disulfiram group, 12 had intestinal and 10 had urinary bladder tumors. In the BF-calcium chloride group, intestinal tumors arose in 16/23 rats and urinary bladder tumors in 4/23 rats, whereas in the 28 BF-PVP rats, 26 exhibited tumors of the intestine and 5, urinary bladder tumors. Dietary BHA, disulfiram, and calcium chloride decreased the incidence of intestinal tumors by about 25%-30%. Similarly, PVP and calcium chloride inhibited BF-induced urinary bladder carcinogenesis by about 80%. No tumors were detected in groups receiving either the normal diet or the normal diet supplemented with BHA, disulfiram, calcium chloride, or PVP. (52 refs.)

**78-0123 Pleural Calcification and Associated Pathology Related to Asbestosis. Study of 32 Cases.** (Fre) Moigneteau, C. (Centre hospitalier et universitaire de Nantes, Hopital Laennec, 44035 Nantes Cedex, France); Touzeau, P. Y.; Guillemin, J. M. *Poumon Coeur* 33(2): 101-105; 1977.

Four neoplasms (2 pleural mesotheliomas, 1 bronchial carcinoma, 1 metastatic hepatoma with unknown primary) developed in a series of 32 men with asbestosis. During a 2-yr follow-up, two additional men developed lung cancer (1 small cell, 1 malphigian type). The 32 men ranged in age from 48 to 84 yr (av 60 yr), and they had been exposed to asbestos occupationally for an av of 27 yr. Twenty-seven had worked in shipyards, 7 in machinery industry, and 4 in construction. Smoking history was obtained in 28 men: 22 were smokers (5, heavy smokers), and 6 were nonsmokers. Respiratory disease, including tuberculosis (2), asthma (1), chronic bronchitis (5), and pleurisy (3), preceded asbestosis in 10 instances. Pleural calcifications indicating the presence of asbestosis were observed on x-rays taken in 20 men for routine examination, in 6 because of bronchial infections, in 2 because of pleural effusion, and in 4 when malignancy was suspected. The three men with bronchial neoplasms discovered coincidentally with asbestosis died within the follow-up period. Other than the two men who developed neoplasms and one who developed serofibrinous pleurisy, none of the other men with asbestosis followed for 2 yr or more developed additional pathology. (28 refs.)

**78-0124 Asbestosis. A Case History.** (Fre) Malauzat, C. (Centre-medico-chirurgical national "Alfred Leune," Mutuelle generale de l'Education nationale 23370 Sainte Feyre, France); Petit, M. A.; Ramaroson, J.; Bourzai, M.; Gaultier, G. *Poumon Coeur* 33(5): 321-330; 1977.

A detailed case history is presented of a 66-yr-old man who developed a pleural mesothelioma after 44 yr of exposure to asbestos. Also, literature on the pathology of asbestos exposure is reviewed from the aspects of types of asbestos and the industries involved, the histology of exposed lung tissue, clini-



cal signs of benign or malignant pathology, and pathogenesis. The initial diagnosis in the case of the asbestos worker was tuberculosis, based on a positive skin test, radiographic evidence of small calcifications in the lung, and a history of progressive dyspnea and thoracic pain. Treatment with broad-spectrum antibiotics failed to improve the patient, and asbestosis was suspected. Bronchial aspiration and sputum analyses revealed asbestosis bodies. An open-thorax biopsy was performed, and the pulmonary tissue showed asbestosis, silicosis, pulmonary tuberculosis, and a pleura mesothelioma. (41 refs.)

- 78-0125 The Biological Effects of Magnesium-Labeled Chrysotile Asbestos.** (Eng) Morgan, A. (Environmental and Medical Sciences Div., Atomic Energy Res. Establishment, Harwell, Didcot, Oxon, England); Davies, P.; Wagner, J. C.; Berry, G.; Holmes, A. *Br J Exp Pathol* 58(5): 465-473; 1977.

Protein adsorptive capacity, hemolytic activity, and capacity to cause selective release of acid hydrolases from macrophages were measured for various Mg-depleted samples of chrysotile asbestos. Albumin adsorption decreased linearly with leaching of Mg, so that when 93% of the Mg had been removed, < 10% adsorption occurred. Hemolytic activity decreased until about 50% of the Mg had been removed, after which little change was noted. Leaching of  $\leq 55\%$  of the Mg increased selective release of the acid hydrolases significantly, but by 90% depletion, release had declined rapidly. Chrysotile samples in which 0%, 50%, and 95% of the Mg had been leached were injected into the pleural cavity of Wistar rats at a dose of 20 mg/rat. In animals receiving intact and 50%-depleted chrysotile, the incidence of mesothelioma was similar: 12/32 and 13/32 developed tumors, respectively. At 95% depletion, only 2/31 developed tumors. However, survival was slightly longer in the group receiving the 50% sample. Electron micrographs of the tumors indicated that leaching did not weaken the fibers, which would have led to their fragmentation in the tissue. Thus, leaching chrysotile of Mg produces marked changes in its biological and structural activity in vivo and in vitro. (20 refs.)

- 78-0126 Alterations of the Fine Structure and Epoxide Values of the Rat Liver After a Vinyl Chloride Monomer Exposure (Meeting Abstract).** (Eng) Takahama, M. (Dept. Pathology, Saitama Medical Sch., Saitama, Japan); Nishibe, Y.; Muraishi, M. *J Electron Microsc (Tokyo)* 26(3): 230; 1977. (no refs.)

- 78-0127 Carcinogenicity Bioassays of Vinylidene Chloride: Research Plan and Early Results.** (Eng) Maltoni, C. (Inst. Oncology and Tumour Centre, Bologna,

Italy); Cotti, G.; Morisi, L.; Chieco, P. *Med Lav* 68(4): 241-262; 1977.

Early results (82-93 wk) of long-term carcinogenicity bioassays of vinylidene chloride (VDC) are presented. VDC was administered by inhalation to Sprague-Dawley rats (200-150, 100, 50, 25, and 10 ppm), Swiss mice (200, 100, 50, 25, and 10 ppm), and Chinese hamsters (25 ppm) and by ingestion to rats (20, 10, 5, and 0.5 mg/kg body wt in olive oil by stomach tube). The treatment was given four to five times per week for 1 yr. In the mice, inhalation at 200, 100 and 50 ppm was discontinued after a few days because of excessive acute toxicity. In rats exposed to VDC by inhalation, the incidence of mammary tumors was higher among treated animals than in controls. No increase in mammary tumors was seen in rats given VDC by intubation. The most important result was the onset of kidney adenocarcinomas in mice exposed to 25 ppm. Male mice appeared to be more responsive than females. This tumor was not observed in mice exposed to 10 ppm or in the other treated species. No tumors were found in the hamsters. In vivo and in vitro studies indicate that VDC is probably metabolized by epoxidation into a more reactive compound that is responsible for its toxic mutagenic and carcinogenic effects. The rate at which active metabolites are formed and metabolized seems to depend on the dose of VDC as well as on the metabolic pathways of the test animals. These pathways appear to be influenced by species and sex. (15 refs.)

- 78-0128 Metabolism of Vinyl Chloride: Destruction of the Heme of Highly Purified Liver Microsomal Cytochrome P-450 by a Metabolite.** (Eng) Guengerich, F. P. (Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN 37232); Strickland, T. W. *Mol Pharmacol* 13(6): 993-1004; 1977.

The NADPH-dependent, vinyl chloride (VC)-mediated destruction of cytochrome P-450 (Cy P-450) was demonstrated in rat liver microsomes and in highly purified reconstituted enzyme systems containing NADPH cytochrome P-450 reductase and cytochrome Cy P-450. This loss of Cy P-450 could be attributed to heme destruction, but not to lipid peroxidation or binding of electrophiles to free sulfhydryl groups. The system required all the components necessary for mixed-function oxidation, including molecular oxygen, and it was inhibited by carbon monoxide, suggesting strongly that oxidative metabolism of VC by Cy P-450 is necessary for destruction. The NADPH Cy P-450 reductase-catalyzed destruction of free and Cy P-450-bound heme was also observed in reconstituted systems in the absence of VC. Inhibition experiments with carbon monoxide and catalase suggested that the VC-mediated destruction of Cy P-450 heme differs from these processes. Two proposed VC metabolites, VC epoxide and 2-chloroacetaldehyde, do not appear to be responsible for the heme destruction. Evidence for the involvement of free radicals could not be demonstrated when the reaction was



examined by electron paramagnetic resonance spectroscopy when attempts were made to inhibit Cy P-450 destruction with radical-trapping agents. (56 refs.)

**78-0129 Uptake and Rate of Metabolism of Vinyl Chloride by the Isolated Perfused Rat Liver Preparation.** (Eng) Radwan, Z. (Inst. Toxicology, Univ. Wurzburg, Versbacher Landstrasse 9, D-8700 Wurzburg, W. Germany); Wenzschler, D. *Int Arch Occup Environ Health* 40(2): 101-110; 1977.

The metabolism of vinyl chloride (VC) under controlled, steady-state exposure conditions in varying concentrations was examined in the isolated perfused rat liver. The solubility of VC in the RBC perfusion medium at 37 C was constant from 50 to 25,000 ppm. The amount metabolized, (14.6%) was determined by the difference between VC concentrations before and after passage of the liver, was also constant throughout this concentration range. This indicates that there is no saturation of those enzymes that initiate metabolic conversion of VC. Ethanol (constant addition to 12 mM) and diazole (single addition to 200  $\mu$ M) reduced VC metabolism to 12.7% and 31.6%, respectively. Bromobenzothiazole also inhibited metabolism (48.9%), SKF 525A was inactive, and phenobarbital pretreatment increased the conversion rate by 1.9%. Fasted animals showed a 31.2% increase in the metabolic conversion rate. Determination of SGOT, SGPT, and the lactate/pyruvate coefficient revealed no VC-induced changes, even at the highest concentration tested (24,000 ppm), but slight liver damage was detectable after increased metabolic VC transformation. This suggests the formation of a reactive intermediate, an epoxide, as a result of the first-step oxidation. The epoxide would be expected if the oxidation were catalyzed by cytochrome P-450. The involvement of other oxidases, however, cannot be ruled out. (19 refs.)

**78-0130 Scintigraphy of Liver and Spleen in Vinyl Chloride Workers.** (Eng) Biersack, H. J. (Institut für Klinische und Experimentelle Nuklearmedizin, 5300 Bonn-Nord, Germany); San Luis, T.; Lange, C. E.; Thelen, G.; Veltman, G.; Winkler, C. *Acta Hepatogastroenterol (Stuttg)* 24(5): 357-361; 1977.

The ability of liver and spleen scintigraphy with  $^{99m}$ Tc-sulfur colloid and  $^{203}$ Hg-BMHP to detect vinyl chloride-induced changes was investigated in (1) 124 workers with 0.5 to 21 yr experience in the production of polyvinyl chloride (PVC) and (2) 28 workers with 1.5 to 18.5 yr experience in the processing of PVC. Of the Group 1 workers, 101 had pathological alterations in the liver and spleen: liver fibrosis (30), hepatomegaly (7), atypical liver configuration (49), nonhomogeneous colloid uptake (62), splenomegaly (59), increased splenic uptake of colloid (83), and an altered bromsulphalein (BSP) test (79). Three filling defects were subsequently diagnosed as angiosarcomas. Portal venous per-

fusion was reduced in seven patients with esophageal varices. Eighteen of the Group 2 workers had similar but less-pronounced pathological changes: hepatomegaly (2), atypical liver configuration (7), nonhomogeneous colloid uptake (7), splenomegaly (15), increased splenic uptake of colloid (17), and an altered BSP test (12). These findings indicate that scintigraphy is valuable in detecting PVC-induced liver and spleen pathology. (22 refs.)

**78-0131 Vinyl Chloride: Hepatic Angiosarcoma Associated with Acroosteolysis.** (Fre) Legrand, J. (No affiliation given); Puech, A. M. *Arch Mal Prof* 38(6): 645-646; 1977.

A 42-yr-old man developed acroosteolysis and an angiosarcoma of the liver after a relatively brief exposure to vinyl chloride. He had developed edema of arms and hands after only 2 yr occupational exposure to vinyl chloride. Ten years later, he again took a job involved with the carcinogen and the acroosteolysis occurred. Symptoms of the angiosarcoma appeared 17 yr after initial exposure, and the patient died within 2 yr. (no refs.)

**78-0132 Factors That Modify the Rate and Extent of Spontaneous Metastases of Prostate Tumors in Rats.** (Eng) Pollard, M. (Lobund Lab., Univ. Notre Dame, Notre Dame, IN); Burleson, G. R.; Luckert, P. H. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 357-366; 1977.

The effects of *Corynebacterium parvum*, aspirin, inhaled anesthetic agents (chloroform, halothane, and ether), and sodium barbiturate on the metastasis of two adenocarcinomas (I and III) of prostate origin were studied in Lobund Wistar rats. The spread of prostate tumors was retarded by regimens involving *C. parvum* and aspirin. Spleens and livers in all of the *C. parvum*-treated rats were significantly enlarged and the livers showed perivascular aggregations of mononuclear cells. There were no significant differences in wts of bodies, tumors, or livers between the aspirin-treated group and controls. The inhalation of chloroform or halothane and the ingestion of sodium diethylbarbiturate resulted in increased numbers of metastatic tumors. In the rats treated with sodium diethylbarbiturate, body wt was essentially the same as that of controls, but livers were heavier in the drug-treated rats. There were no significant differences between rats treated with anesthetic agents and controls in size. The results indicate that metastasis involves a complexity of mechanisms or that *C. parvum* and aspirin share some physiological effects on the tumor cells that have not yet been revealed. (13 refs.)



- 78-0133 **Depression of Macrophages in Mice Drinking Hyperchlorinated Water.** (Eng) Fidler, I. J. (Basic Res. Program, NCI-Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701). *Nature* 270(5639): 735-736; 1977.

The possibility that hyperchlorination (25-30 ppm) of drinking water could adversely affect murine peritoneal exudate macrophages (PEM) was investigated, because difficulties occurred in the collection and in vitro activation of PEM at about the same time that chlorine levels in the water of the animal facility had been increased. C57BL/6N female mice were given tap water or hyperchlorinated water. Just before treatment, the number of peritoneal exudate cells (PEC) per mouse was  $21 \times 10^6$ . Two weeks later, (when the mice were 8 wk old) the number had decreased to  $13 \times 10^6$  in mice receiving hyperchlorinated water but had increased to  $25 \times 10^6$  in mice on tap water. PEM from mice on the two regimens were assayed for in vitro tumoricidal properties. PEM from mice on tap water treated in vitro with lymphokines produced by Concanavalin A stimulated lymphocytes were cytotoxic to syngeneic tumor target cells. PEM collected from hyperchlorinated mice had significantly lower levels of cytotoxicity during the first 2 wk of treatment, and they were not tumoricidal by the third. It is concluded that the addition of high levels of chlorine to the drinking water of mice produces profound alterations in the numbers of PEM and tumoricidal function. The findings raise the possibility that host resistance against neoplasms may also be compromised by hyperchlorinated drinking water. Chlorinated water may reduce the tumoricidal activity of murine macrophages by (1) inhibiting hexose monophosphate shunt metabolism or (2) inhibiting lysosomal enzymes as the result of damage to RBC and the production of hemoglobin degradation products in the macrophage vacuolar system. (21 refs.)

- 78-0134 **Cystic Cholangiofibrosis of the Liver.** (Eng) Dominis, M. (Bolnica, O. Novosel, Zajeeva ul. 19, Zagreb, 41000 Yugoslavia); Damjanov, I. *Arch Geschwulstforsch* 47(7): 661-669; 1977.

The ultrastructure of the epithelium lining the cholangiofibrotic cysts of female Wistar rat liver induced by a discontinuous 14 wk diet of 0.05% N-acetylaminofluorene (AAF) was examined. Following the feeding period, the animals were maintained on a regular laboratory diet for 20 wk and sacrificed. Postnecrotic cirrhosis that developed concomitantly with the hepatocellular changes persisted after cessation of carcinogen administration. Five animals had large cysts throughout the liver containing fluid under pressure. The large cysts were lined by flattened epithelium. Connective tissue around the cysts contained small cysts and bile ductules lined by cuboidal epithelium. The cuboidal cells had an elongated nuclei with frequent invaginations. Most of the cellular organelles were in the supranuclear position. Each cell contained a well developed Golgi apparatus; endoplasmic reticulum was scarce and free ribosomes were scattered

throughout the cell. Some of the cells had a moderately developed smooth endoplasmic reticulum. Flattened epithelium in the distended cysts had the same features as the cuboidal cells except there was less cytoplasm and the nuclei were flattened. Ductules occasionally appeared as lacunar extensions of the cysts with cuboidal cells interconnected with the flattened cells in the cysts. These results suggest that the cysts are of cholangiocellular origin. (10 refs.)

- 78-0135 **Lack of Susceptibility of F344 Rats to Mammary Tumor Induction by Topically Applied Fluorenylacetoxyhydroxamic Acids and Their Acetates.** (Eng) Malejka-Giganti, D. (Veterans Admin. Hosp., 54th St. and 48th Ave., South, Minneapolis, MN 55417); Rydell, R. E. *J Natl Cancer Inst* 60(2): 433-435; 1978.

The carcinogenicity of N-hydroxy-N-3-fluorenylacetylamide (N-OH-3-FAA) for the mammary glands of female inbred F344 rats was examined after systemic and topical administration (2.3 mg/100 g, ip, and 0.02 millimoles, respectively). When given ip, the compound produced a 60% mammary tumor incidence but it was only marginally active after topical application. Female F344 rats did not develop mammary tumors after topical application of N-hydroxy-N-2-fluorenylacetylamide, N-acetoxy-N-2-fluorenylacetylamide, or N-acetoxy-N-3-fluorenylacetylamide. These results contrast with those reported earlier for female Sprague-Dawley rats and indicate strain differences in response to the same carcinogens. (25 refs.)

- 78-0136 **Inhibitory Effect of Hypothalamic Lesions on Liver Tumor Induction by N-2-Fluorenylacetylamide in Male Rats.** (Eng) Toh, Y. C. (Dept. Physiology, Univ. New England, Armidale, New South Wales 2351, Australia). *Cancer Res* 38(1): 42-51; 1978.

The role of the hypothalamus in liver tumor induction by N-2-fluorenylacetylamide (NFA) was investigated in male albino Wistar rats. Hypothalamic lesions were induced in some rats by inserting electrodes in the hypothalamus and passing a direct current of 4 milliamps through the electrodes for 15 sec. Other rats were allocated to sham-operated and untreated control groups. After two wk, 50% of the animals in each group were given 0.03% NFA in the diet for 4-wk periods separated by 1-wk intervals until the carcinogen had been administered for 16 wk. The rats were killed 34 wk after the last carcinogen feeding. Regardless of NFA treatment, livers of some rats with lesions in the median eminence of the hypothalamus contained fat droplets that caused cells to rupture and form fatty cysts. Among the animals fed NFA, none of the 16 with hypothalamic lesions developed hepatomas in contrast to 5/13 sham-operated rats and 6/14 controls. Three operated, NFA-treated rats had areas of cellular alteration; 2 controls and 1 sham-operated rat had neoplastic nodules.



respective of carcinogen treatment, testicular atrophy, inactive thyroid glands, and shorter nasoanal lengths were observed in rats with hypothalamic lesions. The results demonstrate that lesions in the median eminence of the hypothalamus inhibit NFA-induced hepatocarcinogenesis in male rats. (62 refs.)

**0137 Hexamethylene Bisacetamide Induces Morphologic Changes and Increased Synthesis of Procollagen in Cell Line from Glioblastoma Multiforme.** (Eng) Rabson, A. S. (Lab. Pathology, NCI, Bethesda, MD 20814); Stern, R.; Tralka, T. S.; Costa, J.; Wilczek, J. *Proc Natl Acad Sci USA* 74(11): 5060-5064; 1977.

The effect of 5 mM hexamethylene bisacetamide (HB; diacetyldiaminohexane) on a malignant mesenchymal cell line (BT) derived from a 49-yr-old woman with glioblastoma multiforme was investigated. After 10 to 14 days of treatment, the cultures developed a whorled pattern that increased as cultures maintained for 21 to 28 days. No effects were observed with 0.5 mM HB; 50 mM HB killed the cells within 24 hr. The most striking ultrastructural effect of HB treatment was a marked increase in extracellular 220-A fibrils. Cells treated for 21 days had a 500% increase in proline incorporation into proteins of the cell supernatants. HB also increased procollagen synthesis, mainly that of type I, within 24 to 40 hr of treatment; a max effect was noted after 7 days, when the rate was 20 times greater than that of controls. HB had no effect on the procollagen synthesis of normal human fibroblasts obtained by punch biopsy. (15 refs.)

**0138 Damage and Repair of DNA in Cultured Mamalian Cells with N-Diazoacetyl glycine Amine.** (Eng) Parodi, S. (Dept. Oncology, Genoa Univ., 16132 Genoa, Italy); Bolognesi, C.; Cavanna, M.; Pollack, R. L.; Monti, L.; Brambilla, G. *Cancer Res* 37(12): 4460-4466; 1977.

DNA damage and repair were studied in cloned BALB/c mouse kidney cells treated with N-diazoacetyl glycine amide (DGA). As demonstrated by autoradiography, DGA (0.62 mM) induced prolonged, dose-dependent, unscheduled DNA synthesis. According to alkaline sucrose gradient sedimentation analysis, there was a linear relationship between the number of single-strand breaks and DGA concentration. The number of breaks was max after 1 hr of treatment and remained constant or decreased only slightly during the 68-hr treatment interval. A significant number of breaks occurred after incubation of the cells at 4°C in hypotonic EDTA solution, which suggested that DGA does not require metabolic activation. The presence of DNA damage and the sluggish DNA repair at nontoxic DGA doses could be related to the carcinogenic and mutagenic properties of this compound. (29 refs.)

**0139 Histologic and Histochemical Preneoplastic Changes in the Bladder Mucosae of Dogs Given**

**2-Naphthylamine.** (Eng) Radomski, J. L. (Dept. Pharmacology, Univ. Miami, Sch. Medicine, P.O. Box 520875, Biscayne Annex, Miami, FL 33152); Krischer, C.; Krischer, K. N. *J Natl Cancer Inst* 60(2): 327-333; 1978.

To determine the mechanism of action of the N-hydroxy metabolite of 2-naphthylamine (2-NA) on bladder epithelium, an attempt was made to detect the earliest cellular changes produced by this carcinogen. Four purebred beagle dogs were given a highly carcinogenic dose of 2-NA (25 mg/kg/day, 5 days/wk) for 1, 6, and 36 wk. Epithelial changes began with erosion of the surface cells and disruption of the luminal membrane, which were seen by light and electron microscopy as early as 1 and 6 wk. Other early changes, i.e., hyperplasia, loss of alkaline phosphatase activity in the basal cells, and lymphocytic infiltration, did not occur with any consistency until 36 wk after treatment. The initial histologic effects were similar to the classic picture of simple chronic irritation. Scalloping of the basal cell layer, due to the start of nodule formation of the hyperplastic epithelial cells (von Brunn's epithelial nests), was not observed until after 36 wk of treatment. No tumors were noted in these dogs. However, 2/4 dogs given 2-NA for 26 wk and then kept for 3 yr developed epithelial carcinomas. This suggests that the early changes observed in the first experiment are probably associated with cancer induction. In addition, tumor development long after cessation of treatment with carcinogen further establishes the validity of the dog as an experimental model for human bladder cancer, which has a similar schedule of appearance. (27 refs.)

**78-0140 Carcinogenicity of Diazoacetic Ester (DAAE) (Meeting Abstract).** (Eng) Love, L. A. (Eppley Cancer Res. Inst., Univ. Nebraska Medical Center, Omaha, NB); Pelfrene, A. F.; Garcia, M. G. *Anat Rec* 189(3): 547-548; 1977. (no refs.)

**78-0141 Effect of Propylthiouracil on Intestinal Tumor Formation by Azoxymethane in Rats.** (Eng) Singh, D. V. (Div. Toxicology, HFF-152, Food and Drug Administration, 200 C St., S. W., Washington, DC 20204); Campbell, R. L.; Lin, Y. N.; Nigro, N. D. *Experientia* 33(11): 1516-1518; 1977.

The administration of propylthiouracil (PTU, 0.05% in the diet) for 24 wk to Sprague-Dawley rats given weekly sc injections of azoxymethane (8 mg/kg) resulted in a significant decrease in intestinal tumors (68 neoplasms in 20 rats vs 167 in 20 rats not given PTU). PTU treatment also significantly decreased the total concentration of fecal bile acids and the concentrations of the neutral steroids cholesterol and coprostanol. Thus, the hypothyroid state induced by PTU may affect intestinal carcinogenesis in this animal model by lowering the fecal bile acid and neutral steroid concentrations. (24 refs.)



- 78-0142 Experimental Studies on Sites of Tumor Development in the Intestine by Chemical Carcinogens.** (Eng) Hirono, I. (Dept. Carcinogenesis and Cancer Susceptibility, Inst. Medical Science, Univ. Tokyo, Tokyo, Japan); Shibuya, C.; Fushimi, K. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp.; 285-295; 1977.

The site of tumor development in the intestine was studied in two experiments. In the first, male Sprague-Dawley rats received either one iv injection of 25 mg/kg methylazoxymethanol (MAM) acetate or weekly injections for 5 or 15 wk. Only 3/13 single-dose animals developed tumors in the jejunum and ileum (4 tumors), and only 1 developed a tumor in the colon and rectum. In the 14 animals receiving injections for 5 wk, there were 158 tumors: 10 rats had 48 tumors in the jejunum/ileum, 13 had 103 tumors in the colon/rectum, 5 had 6 tumors in the cecum, and 1 had 1 tumor in the duodenum. In the last group, 11 animals had 362 tumors: 6 rats had 20 tumors of the jejunum/ileum; 10 had 315 tumors in the colon/rectum; and 5 each had duodenal (8) and cecal (19) tumors. In further studies, male Sprague-Dawley rats were given cycasin one intragastric dose of 80 mg/kg (I) or 250 mg/kg (II), or 15 weekly doses of 80 mg/kg (II). There was 1 tumor of the colon/rectum in 1/15 rats in Group I; 6 tumors of the colon/rectum, 3 of the jejunum/ileum, 2 of the duodenum in 6/13 rats in Group II; 29 tumors of the colon/rectum, 15 of the jejunum/ileum in 11/12 rats in Group III. It is suggested that MAM acetate is metabolized by the liver and that the products in the bile exert the carcinogenic action. MAM transformed from cycasin presumably reacts through the methyl carbonium ion. In the second study, ACI rats either had 20 cm of anal ileum removed, the cecum removed, or 20 cm of anal ileum and cecum removed, and all groups were fed bracken powder for 90 days (1 part bracken: 2 parts basal diet). In all treatment groups, intestinal tumors occurred most frequently in the terminal 20 cm adjacent to the anastomosis. This suggests that the section of small intestine prone to stagnation is where bracken-induced tumors are produced. (9 refs.)

- 78-0143 The Adaptation of Short-Term Assays for Carcinogens to the Gastrointestinal System.** (Eng) Stich, H. F. (Dept. Medical Genetics, Univ. British Columbia, Vancouver, British Columbia, Canada); Koropatnick, D. J. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan) 441 pp.; 121-134; 1977.

The usefulness of DNA fragmentation and DNA repair synthesis as indicators of in vivo carcinogenicity was explored. Alkaline sucrose gradient analysis of whole organs was used to detect unscheduled DNA synthesis. DNA repair was

recognized by a return of small molecular DNA to its original position in the sucrose gradient. Rats exposed to methylazoxymethanol (25 mg/kg), dimethylnitrosamine (DMN; 10 mg/kg) N-methyl-N-nitrosourea (80 mg/kg), or methylmethanesulfonate (120 mg/kg) showed fragmentation of the liver DNA followed by a partial return of the fragment to the original position. However, the sedimentation shifts toward high mol wts varied greatly. When these methods were applied to the gastrointestinal tract, repair synthesis could be readily distinguished from scheduled synthesis by both the location and extent of thymidine labeling. Comparison of 4-nitroquinoline 1-oxide, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and N-acetoxy-2-acetylaminofluorene with DMN and 2-acetylaminofluorene (2-AAF) indicated that only the ultimate carcinogens can induce DNA fragmentation in the epithelium of the esophagus, cardiac and pyloric stomach, and small intestine. Neither DMN nor 2-AAF elicited repair. These results are in agreement with autoradiographic data. A single dose of MNNG resulted in a pronounced shift of the DNA profiles followed by return of a major portion of the low-mol wt DNA to the original position. Studies of boiling water extracts of bracken fern, either force-fed to mice or poured over cultured fibroblasts, indicated that boiling removes much of the carcinogenic activity. (38 refs.)

- 78-0144 Studies in Rat with the Carcinogen Methylazoxymethanol Acetate: Mechanism of Inhibition of Hepatic Protein Synthesis and of Organotropy (Meeting Abstract).** (Eng) Grab, D. J. (Cornell Univ. Medical Coll., Ithaca, NY). *Diss Abstr Int [B]* 38(5): 1998B-1999B; 1977. (1 ref.)

- 78-0145 Methylation of Intestinal and Hepatic DNA in Rats Treated with Methylazoxymethanol Acetate.** (Eng) Zedeck, M. S. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Brown, G. B. *Cancer* 40(5, Suppl): 2580-2583; 1977.

The relationship between tumor induction with methylazoxymethanol acetate (MAM) and DNA methylation was investigated by measuring the levels of 7-methylguanine in the DNA isolated from the duodenum, descending colon, and liver of male Sprague-Dawley rats treated with various doses of the carcinogen. By 3 hr after carcinogen treatment, the level of 7-methylguanine in the liver increased from 2 to 9.2 parts per thousand of guanine as the MAM dose was increased from 20 to 140 mg/kg. Furthermore, at doses of 20 and 35 mg/kg, there was a relationship between the extent of DNA methylation and the time of sacrifice after treatment. In contrast, 7-methylguanine in samples of intestinal DNA was hardly detectable, even at doses of MAM as high as 140 mg/kg. These data suggest that the 7-methylguanine level does not correlate with sensitivity to tumor induction by MAM. (14 refs.)



**78-0146 Enzyme Variants in Normal and Neoplastic Intestinal Mucosa.** (Eng) Trotta, P. P. (Lab. Cell Metabolism, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Balis, M. E. *Cancer* 40(5, Suppl): 2592-2599; 1977.

The properties of adenosine deaminase in normal intestine and in neoplastic tissue induced by iv injection of 35 mg/kg methylazoxymethanol acetate into male CFN rats were investigated. Adenosine deaminase activity in the rat was also compared with that in humans and in mice. Normal rat colon possessed predominantly one electrophoretic variant. Tumors showed the appearance of an additional form with a lower isoelectric point (PI). The normal enzyme and the two tumor forms could be distinguished by their relative substrate specificity and their sensitivity to inhibition by 9-erythro-2-hydroxy-3-nonyladenine. The two tumor enzymes could also be distinguished by their specificity for 9- $\beta$ -D-arabinofuranosyladenine. The enzyme from normal jejunum had two variants that exhibited pI values of 4.85 (ADase I) and 4.80 (ADase II). The relative proportions of these forms differed in mitotically active and differentiated cells. The form with the higher isoelectric point predominated in the tip cells and was similar to the variant observed in the tumors. The specific activity in the tip cells was also severalfold higher than that in the crypt regions. The mol wts of forms I and II were 37,500 and 33,500, respectively. Cycloheximide dramatically decreased tip enzyme activity and abrogated the dominance of ADase I in the tip cells. It is concluded that ADase I in the differentiated cells is related to protein synthesis and that changes in the normal enzyme are related to normal growth and differentiation in the intestines. (32 refs.)

**78-0147 DNA Repair Synthesis in Mouse Mammary Tissue Treated with Alkylating Agents (Meeting Abstract).** (Eng) Bodell, W. J. (Univ. Nebraska, Lincoln, NB). *Diss Abstr Int [B]* 38(5): 2032B-2033B; 1977. (no refs.)

**78-0148 Antigenic Cross reactivities of Rat Neurogenic tumors Induced by Ethylnitrosourea Tested by Capillary Migration Inhibition Test.** (Eng) Oda, Y. (Dept. Neurosurgery, Kyoto Univ. Medical Sch., Kyoto, Japan); Handa, H.; Kieler, J. *Arch Jpn Chir* 46(5): 521-529; 1977.

The antigenic cross-reactivities of Wistar rat neurogenic tumors induced by ethylnitrosourea (ENU) were examined by the capillary migration inhibition test. The tumors were a peripheral nerve neurinoma (T1), two trigeminal nerve neurinomas (T2 and T3), and a mixed glioma (T4). All tumors showed some cross-reactivity with lymphoid cells (thymus and lymph node cells) from the original tumor-bearing hosts or from rats hypersensitized with mitomycin-treated tumor cells. However, the intensities of the reactions differed. In addition to reacting with all the ENU-induced tumors, T1-sensitized lymphoid cells reacted with 1-wk fetal and adult brain tissues; they did not react with 2-wk fetal tissue,

a spontaneous mammary tumor, or adult liver. T3-sensitized lymphoid cells reacted with T1, T3, and T4, the mammary tumor, and 1- and 2-wk fetal tissues, but not with T2, adult brain, or adult liver. T2-sensitized lymphoid cells reacted only with T1 cells. The results suggest that these tumors share a common antigen that is not present in normal brain or 2-wk fetal tissue. (19 refs.)

**78-0149 Induction and Transplantability of Rat Neurogenic Tumors.** (Eng) Oda, Y. (Dept. Neurosurgery, Kyoto Univ. Med. Sch., Kyoto, Japan); Handa, H.; Kieler, J. *Acta Jpn Chir* 46(5): 513-520; 1977.

Ninety-six neurogenic tumors were induced in Wistar rats by the transplacental administration of ethylnitrosourea (ENU: single ip injection of 60 mg/kg) in late fetal life. The most common tumors were malignant neurinoma (41%) and oligodendroglioma (25%). Dimethylbenzanthracene (15 mg/kg) administered the same way as ENU failed to induce neurogenic tumors. Seven ENU-induced neurogenic tumors were maintained by serial transplantation. In the first transplantation generation, some tumors with the same histological pattern differed markedly in growth rate. This may have been a reflection of differences in the antigenicity of the tumors. After the second generation, each histologic type tended to exhibit the same latency and life-span. (23 refs.)

**78-0150 Neuroblasts in Cerebral Tumors Induced by Ethylnitrosourea in Rats.** (Eng) Lantos, P. L. (Dept. Neurological Studies, Middlesex Hosp. Medical Sch., Mortimer St., London W1N 8AA, England); Pilkington, G. J. *Virchows Arch [Cell Pathol]* 25(3): 243-259; 1977.

Pregnant BD-IX rats were given a single iv injection of 30 mg/kg N-ethyl-N-nitrosourea (ENU) on gestation day 15. Twenty-seven of the 40 offspring developed cerebral tumors, all malignant gliomas (astrocytomas, oligodendrogliomas, mixed oligodendroastrocytomas, ependymomas, anaplastic gliomas, and periventricular pleomorphic gliomas). Two medullary pleomorphic gliomas contained neuroblastlike cells, ie, large polygonal cells containing large oval nuclei with prominent nucleoli. They were arranged in groups, cords, and rosettes, patterns similar to those found in ependymomas, except that the constituent cells and their nuclei and nucleoli were larger. The cytoplasm contained parallel arrays of rough-surfaced endoplasmic reticulum, many free ribosomes and polysomes, and occasional subsurface cisternae. The Golgi complexes, situated near the nucleus, were well-developed: their dilated cisternae and abundant vacuoles and vesicles suggested high activity. The cytoplasm extended into processes of various sizes, some of which contained microtubules and filamentous material. Neurosecretory granules 110-200 nanometers in diameter were present in some cells. They had a central dense core surrounded by a halo and enveloped by a single membrane. The presence of the neuroblasts suggests that neurones or their precursors, and not only



glial cells, are susceptible to the carcinogenicity of ENU. However, the incidence of neuronal tumors induced transplantably by ENU is low. This fact may be due to the rapid elimination of ethylated DNA from the neuronal cells or to a difference in DNA replication in neurones and glial cells. (43 refs.)

**78-0151 DNA Repair and Chromosome Aberrations in Human Cells Infected with LPV Oncornavirus.** (Rus) Andzhaparidze, O. G. (Scientific Res. Inst. Viral Preparations, Moscow, USSR); Shvetsova, T. P.; Vostrova, N. G.; Andreeva, E. N.; Stepanova, L. G.; Zasukhina, G. D.; Avakova, A. N. *Vopr Virusol* (6): 712-716; 1977.

To determine whether oncogenic viruses can enhance the mutagenic activity of chemical carcinogens, a diploid culture of human embryo lung cells (line L-63) was infected with oncornavirus LPV and then treated with N-methyl-N'-nitrosoguanidine (MNNG: 0.1 and 1  $\mu\text{g/ml}$ ) or was irradiated with  $\gamma$  rays (5 kilorads). MNNG-induced DNA breaks in control (noninfected) cells were completely repaired within 20 hr after exposure to the mutagen, but in the infected cells DNA breaks showed only partial repair. Radiation-induced breaks were completely repaired both in infected and non-infected cells. Although, the frequency of MNNG-induced and LPV-induced chromosome aberrations was similar (up to 15% and 14.3%, respectively), chromosome and chromatid exchanges were detected only in cells treated with MNNG. The frequency of chromosome aberrations in cells infected with LPV and treated with MNNG was significantly greater (42%), and it was concluded that the synergistic effect of MNNG and LPV was probably due to inhibition of the repair system by the oncogenic virus. (9 refs.)

**78-0152 Pepsinogens and Stomach Cancer.** (Eng) Furihata, C. (Dept. Molecular Oncology, Inst. Medical Science, Univ. Tokyo, Tokyo, Japan); Tatematsu, M.; Shirai, T.; Yokochi, K.; Takahashi, M.; Sugimura, T. *In: Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 49-63; 1977.

Changes in the pepsinogen isozyme pattern during carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 83  $\mu\text{g/ml}$  in drinking water) in rats were investigated and compared to changes observed during normal development. Of three isozymes normally present in the pyloric mucosa (Pg 1, Pg 3, Pg 4), Pg 1 disappeared or decreased soon after the beginning of treatment. This change was always observed in the pyloric mucosa, and it was associated with histological alterations such as atrophy of the pyloric glands, hyperplasia of the surface epithelium, and development of irregularities in the arrangement of glands. It was observed in adenomas (2) and well-differentiated adenocar-

cinomas of the pylorus (28) and in transplanted 4-nitroquinoline 1-oxide-induced well-differentiated adenocarcinomas of the fundus (2). The isozyme pattern in metaplasia was the same as that in normal pyloric mucosa. During development, the isozyme pattern of the fundic mucosa changed from the fetal type (Pg 1 and Pg 3) to the intermediate infant type (Pg 1, Pg 3, and Pg 4) to the adult type (Pg 1 through Pg 4). The pattern in the pyloric mucosa (Pg 1, Pg 3, and Pg 4) did not change after birth. Comparison of the normal pepsinogen isozyme composition of the fundus and pylorus in humans with adenocarcinomas of these regions indicated that the contents of pepsinogen and cathepsin D-type acid protease in the adenocarcinomas were 5%-10% of those in normal pyloric mucosa. Furthermore, no acid protease activity was detected in a signet ring cell carcinoma. (41 refs.)

**78-0153 Molecular Aspects of Gastrocarcinogenesis, Experimental and Clinical.** (Eng) Kawachi, T. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tokyo, Japan); Matsukura, N.; Sasajima, K.; Kurisu, M.; Sano, T.; Sugimura, T. *In: Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 95-105; 1977.

The presence of sucrase in human samples of intestinal metaplasia and tumor induction in male Wistar rats with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and N-propyl-N'-nitro-N-nitrosoguanidine (PNNG) were investigated. Stomachs with areas of intestinal metaplasia were obtained at gastrectomy. Sucrases from normal small intestine and intestinal metaplasia gave a single band on gel electrophoresis; furthermore, pH activity profiles,  $K_m$ , and  $V_{max}$  were almost the same for the two sucrases. However, only 2/5 enzyme preparations from the intestinal metaplasia showed levels of blood group activity similar to those of sucrase from the small intestine. The kinetic constants and pH activity profiles of the sucrase were the same, indicating that sucrase, from the intestinal metaplasia has similar enzymatic properties to those of sucrase from the small intestine; however the antigenic sugar moiety of the enzyme associated with blood group activity varies. Administration of 83  $\mu\text{g/ml}$  MNNG to rats for 2, 4, 5, or 7 mo revealed that the production of intestinal metaplasia required a shorter term of administration of carcinogen than the production of adenocarcinomas. Treatment of rats with 59.5  $\mu\text{g/ml}$  PNNG for 4, 8, or 12 mo produced metaplasia in those treated for 4 mo, metaplasia and adenoma in those treated for 8 mo, and metaplasia, adenoma, and adenocarcinoma in those treated for 12 mo. These findings suggest that the intestinal metaplasia did not arise from regenerative mucosa. A genetic alteration may be necessary for metaplasia and adenocarcinoma. (26 refs.)

**78-0154 Cancer Risk in Stomachs Resected for Gastric Ulcer. Role of the Duodenogastric Reflux.** (Ger)



Dahm, K. (Abteilung Allgemeinchirurgie der Chirurgischen Universitätsklinik, Martinistrasse 52, D-2000 Hamburg 20, W. Germany); Eichen, R.; Mitschke, H. *Langenbecks Arch Chir* 344(2): 71-82; 1977.

Gastroenteric anastomoses were performed on male Wistar rats to determine whether the reflux of bile and pancreatic juices following stomach resection enhances the incidence of carcinoma near the anastomosis. Thirty-nine rats were subjected to a Billroth II anastomosis, which provides a continuous duodenogastric reflux, and 33 were subjected to a Y-shaped Roux anastomosis, which prevents the bile and pancreatic juices from contacting the remaining portion of the stomach. Operated rats and controls (27) then received 120 mg/liter N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the drinking water. Autopsy was performed 33 to 36 wk later. In the Billroth group, 7 rats had carcinomas at the anastomosis, 4 had carcinomas in the small intestine, and 2 had sarcomas; in the Roux group, one rat had a carcinoma at the anastomosis and 6 had carcinomas in the small intestine. There was one sarcoma in the control group. These findings indicate that in rats, duodenogastric reflux contributes substantially to the development of carcinomas in the resected stomach. (12 refs.)

78-0155 **Follow-up Studies of Experimental Stomach Cancer in Dogs.** (Eng) Saito, T. (Second Dept. Surgery, Kyushu Univ. Sch. Medicine, Fukuoka, Japan); Asaki, O.; Tamada, R.; Iwamatsu, M.; Matsukuchi, T.; Matsukuchi, K. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 107-120; 1977.

Stomach cancer induction in male beagle dogs by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) was studied. Fifteen dogs received 50-83 µg/ml MNNG in the drinking water for 15 to 63 wk; the dogs were followed for 216 wk. Ulcers were present by weeks 30-40, and they began to heal after termination of MNNG. Cancer arose in the area of the scar in two dogs in weeks 97 and 102. One regressed and one was examined endoscopically up to the death of the dog during week 216. By that time, the cancer had progressed to Borrmann's type 3, and it had invaded the serosa and metastasized to a paraceliac lymph node. Four other dogs had cancer and coexisting lesions: 4/6 cancers were located in areas of mucosal atrophy, 1 was in the ulcer scar, and 1 was in the open ulcer. In another experiment, eight dogs received 150 µg/ml ENNG for 1 yr, either in a mixture in the chow or in the drinking water. Erosion was observed in all eight dogs, and ulcers were seen in six. Six dogs developed stomach cancer, four in the area of the ulcer scars and two directly on the open ulcer. The period from the end of ENNG administration until the development of stomach cancer was probably too short to allow ulcer healing. With both carcinogens, the main lesions preceding stom-

ach cancer were erosion, ulcer, atrophy, and ulcer scars. However, these lesions changed with time, and those coexisting with the cancer were not always the preceding ones. (22 refs.)

78-0156 **Carcinogenic Effect of N-Methyl-N'-nitro-N-nitrosoguanidine and Fission Neutron Irradiation in Rats.** (Eng) Vogel, H. H. (Dept. Radiation Oncology, 800 Madison Ave., Memphis, TN 38163); Sebes, J. I. *Gann* 68(5): 627-634; 1977.

The effect of two carcinogens, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 83 mg/liter of drinking water) and whole-body irradiation (WBI) with 200 rads of fission neutrons, on the gastrointestinal tract of male albino Sprague-Dawley rats was evaluated. The rats were divided into five groups: (1) MNNG in drinking water for 7 mo; (2) WBI; (3) WBI followed by MNNG for 7 mo; (4) MNNG for 5 mo followed by WBI; (5) untreated controls. Of the 13 MNNG-treated animals that survived > 9 mo, 9 showed gross tumors (5 gastric, 4 duodenal), confirming the high incidence of gastrointestinal tumors induced by MNNG in the rat. No gastrointestinal tumors were found in Group 2; the seven tumors seen were neoplasms of the skin, mammary glands, and, possibly, liver. At the fifth week after WBI of Groups 2 and 3 rats, there was a dramatic decrease in body wt (av wt loss 50-75 g between weeks 5 and 6). This was caused by the loss of one or more incisor teeth. There were five tumors in the antral region of the stomach or proximal small intestine in Group 3 rats, but in view of the results from Group 1, no evidence for additivity or synergism was found. Group 4 rats seemed in good health at the end of MNNG treatment, but 2 days after WBI, the animals began to die. Within 11 days of exposure, all 24 rats had died. In contrast, Group 3 rats died during the so-called acute radiation period. In conclusion, when the two carcinogens were combined, no additivity or synergism occurred. (24 refs.)

78-0157 **Primary Mitogenic Action of N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG).** (Eng) Danz, M. (Pathologisches Institut der Friedrich-Schiller-Universität, Zieglmühlenweg 1, DDR-69, Jena, E. Germany); Ziebarth, D.; Urban, H.; Schmidt, A. *Exp Pathol (Jena)* 14(1/2): 108-110; 1977.

The mutagenic action of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was investigated in male Sprague-Dawley rats after they received a single dose of 150 mg/kg MNNG by stomach tube. The animals were killed 48 hr after MNNG administration and autopsied. There was a small decrease in body wt resulting from a reduced food uptake, but there was an increase in the wt of the spleen, thymus, and adrenals. An increased mitotic rate in the adrenals agreed with previous findings, but an increased mitotic rate in the liver was not accompanied by necrosis. Since most of the carcinogen was excreted as an inactive metabolite within a few hours, it is doubtful if there is a direct action of the compound



on the liver. Whether the growth stimulation results from hormonal regulation or alterations of a nonspecific growth-inhibitory interaction of various tissues is unknown. (21 refs.)

- 78-0158 Carcinogenicity of N-Nitrosopyrrolidine: Dose-Response Study in Rats.** (Eng) Preussmann, R. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Schmahl, D.; Eisenbrand, G. *Z Krebsforsch* 90(2): 161-166; 1977.

The carcinogenicity of N-nitrosopyrrolidine (NP) was studied in Sprague-Dawley rats given daily doses of 10, 3, 1, or 0.3 mg/kg (NP) in the drinking water. The incidences of malignant tumors in rats fed 10, 3, and 1 mg/kg NP were 46%, 84%, and 32%, respectively. The incidence in the group on the lowest dose was 9.8%, but this was not significant. However, this group did have several benign adenomas that were not found in the controls. The low incidence of tumors in the 10-mg/kg group could be due to the high cumulative toxicity of NP. Hepatocellular carcinomas were the predominant tumor in animals receiving the three largest doses of NP. Treated animals also had a slight increase in the incidence of malignant tumors and leukemias compared to the controls. Survival times for controls and the two lower-dose groups did not differ greatly, suggesting that carcinogen treatment did not significantly shorten the life span of these animals. A review of the literature on the carcinogenicity of NP in other species is presented. (18 refs.)

- 78-0159 Carcinogenic Effect of N-Nitroso-2,6-dimethylmorpholine in Syrian Golden Hamsters.** (Eng) Reznik, G. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Weichert-Allee 9, 3000 Hannover 61, W. Germany); Mohr, U.; Lijinsky, W. *J Natl Cancer Inst* 60(2): 371-378; 1978.

N-Nitroso-2,6-dimethylmorpholine (DMNM) was administered intragastrically once weekly for life to Syrian golden hamsters at four dose levels [74 mg/kg wt = 1/5 LD<sub>50</sub>; 37 mg/kg = 1/10 LD<sub>50</sub>; 18 mg/kg wt = 1/20 LD<sub>50</sub>; and 9 mg/kg = 1/40 LD<sub>50</sub>]. The incidence of pancreatic neoplasms was highest (71%) in males treated with 1/20 of the DMNM LD<sub>50</sub>; these tumors were adenomas or adenocarcinomas of ductal origin. In addition, neoplasms developed in the nasal cavities, larynx, trachea, lung, liver, gallbladder, kidneys, and forestomach, with tumor incidences ranging from 7%-67%. The number of induced tumors was not significantly dose-dependent. (17 refs.)

- 78-0160 Carcinogenic Effect of Subcutaneously Administered N-Nitroso-2,6-dimethylmorpholine in Syrian Golden Hamsters.** (Eng) Althoff, J. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Weichert-Allee 9, 3000 Hannover 61, W. Ger-

many); Grandjean, C.; Gold, B. *J Natl Cancer Inst* 60(1): 197-199; 1978.

The acute and chronic carcinogenic effects of N-nitroso-2,6-dimethylmorpholine (DMNM) when administered sc in Syrian golden hamsters were determined, and the results compared to a previous study in which the compound was administered intragastrically. Acute toxicity experiments, in which 1,000, 500, 250, or 125 mg/kg were administered indicated that the LD<sub>50</sub> was 320 mg/kg (308 for females and 354 for males). Tumors that developed in the animals that survived this test were mainly forestomach papillomas. Chronic effects were examined by inoculating animals with 32, 16, or 8 mg/kg DMNM once weekly for life. All animals were killed by 56 wk. The group receiving 32 mg/kg (30 animals) survived an av of 32 wk; tumor incidence was 100% with tumor appearing mainly in the nasal cavities (97%), vagina (53%) trachea and lung (40% each). The 30 animals receiving 16 mg/kg and a 97% tumor incidence and survived an av of 37 wk. Most tumors were in the nasal cavities (83%) and vagina (80%). The 30 animals receiving 8 mg/kg had a 93% tumor incidence with an av survival of 47 wk. Tumors were mainly in the nasal cavities (80%) and vagina (87%). Compared to intragastric administration, DMNM was more toxic, neoplasms occurred earlier, and fewer tumors of the pancreas and biliary tract were found. Neoplasms of the upper digestive tract and vagina were only seen with sc treatment. Since DMNM is formed by  $\beta$ -oxidation of N,N-dipropyl nitrosamine, these findings indicate the importance of metabolites and method of administration in tumor development. (19 refs.)

- 78-0161 Fine Structure of Cholangiofibromas Induced in the Rat by N-Nitrosomorpholine.** (Ger) Banasch, P. (Abteilung für Cytopathologie, Institut für Experimentelle Pathologie am Deutschen Krebsforschungszentrum Heidelberg, D-6900 Heidelberg 1, W. Germany); Massner, B. *Virchows Arch [Cell Pathol]* 24(4): 295-315; 1977.

The ultrastructural characteristics of 11 cholangiofibromas induced in male Sprague-Dawley rats 20-73 wk after three weekly administrations of a 50 mg% solution of N-nitrosomorpholine were investigated. The tumor epithelium was characterized by mucus-producing tubules surrounded by a basal lamina and containing an apical brush border with marked glycocalyx. Neighboring ductal epithelial cells showed marked interdigitations, and a large number of desmosomes were frequently present. The cytoplasm of the tumor cells was rich in ribosomes and/or a granular endoplasmic reticulum. Golgi bodies were numerous and large; large bundles of tonofilaments developed in many cells. The tubules frequently contained goblet cells that produced acid and neutral mucopolysaccharides; glycogen storage cells were found occasionally. Lipoid bodies were sporadic, but peroxisomes were absent. The mesenchymal portion of the tumor was composed of fibroblasts, collagen fibers, and capillaries. The fibroblasts and endothelial cells frequently con-



ained large bundles of cytoplasmic microfilaments. Mast cells were often found in the tumor tissue. These findings suggest that the tumors were derived from cholangiofibroses and that the epithelial component originated from intrahepatic bile duct epithelia. (48 refs.)

**78-0162 Glycogenolysis in Isolated Rat Hepatocytes during Treatment with N-Nitrosomorpholine** (Meeting Abstract). (Eng) Mayer, D. (Institut für Experimentelle Pathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany). *Hoppe Seylers Z Physiol Chem* 358(10): 1246-1247; 1977. (no refs.)

**78-0163 Nitrosamine Formation in Human Saliva.** (Eng) Tannenbaum, S. R. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Archer, M. C.; Wishnok, J. S.; Bishop, W. W. *J Natl Cancer Inst* 60(2): 251-253; 1978.

Observations of nitrosation in saliva and in saliva mixed with acid, to simulate reaction conditions in the stomach, are reported. The formation of N-nitrosomorpholine (NM) from morpholine (M), a weak base that undergoes rapid nitrosation, was used to study nitrosamine production. In initial experiments, NM formation was examined in whole saliva from several individuals. A low but highly consistent amount of NM was synthesized in all samples. Next, the effectiveness of the various salivary fractions (from a single donor) in the nitrosation of M was determined. After 30 min incubation of the fractions with 1,000 mg/liter M, NM could only be detected in whole saliva [12 nanomoles (nmol)/liter]. Neither the cell-free supernatant, cells resuspended in buffer at pH 7.2, heated whole saliva, nor the buffer control yielded detectable NM. When 100 mg/liter NaNO<sub>2</sub> was added to the M-containing fractions, the resuspended cells produced the greatest amount of NM (188 nmol/liter). The cell-free supernatant and heated whole saliva yielded small amounts that were slightly higher than control levels (5 nmol/liter), and whole saliva produced a third as much NM as the resuspended cells (64 nmol/liter). Salivary fractions containing 1,000 mg/liter M but no NaNO<sub>2</sub> were then acidified to pH 3.0. NM levels were much higher in the acidified fractions, but differences among fractions were noted. NM could not be detected in the control or resuspended cells, but whole saliva, heated saliva, and the cell-free supernatant produced 3,176, 1,857, and 1,676 nmol/liter of NM, respectively. The results show that nitrosamine formation is possible in saliva even at neutral pH and that saliva contains components that both accelerate and retard nitrosamine formation. (20 refs.)

**78-0164 In Vivo Formation of N-Nitroso Compounds and Detection of Their Mutagenic Activity in the Host-mediated Assay.** (Eng) Braun, R. (Zentralinstitut

für Genetik und Kulturpflanzenforschung der Akademie der Wissenschaften der DDR, 4325 Gatersleben, E. Germany); Schoneich, J.; Ziebarth, D. *Cancer Res* 37(12): 4572-4579; 1977.

The formation of N-nitroso compounds in NMRI mice given equimolar doses of sodium nitrite and secondary amines or alkylurea derivatives simultaneously by stomach tube was estimated by determining the mutagenic activity of the compounds to *Salmonella typhimurium* TA1950. Of the secondary amines tested in combination with nitrite, only piperazine dihydrochloride (PZ), morpholine (MOR) and amitrole (AMT) increased mutant frequencies in the bacteria. PZ was the strongest mutant with nitrite, AMT the weakest. No mutagenic activity was observed with equimolar doses of nitrite plus dimethylamine hydrochloride, diphenylamine, methylbenzylamine hydrochloride, or phenmetrazine hydrochloride. All three N-alkylurea compounds tested yielded significant amounts of N-nitroso compounds in combination with nitrite. However, ethylenebis(thiourea) was more mutagenic than methylurea or ethylurea. Dose-response curves for the mutagenicity of N-nitrosamines were used to estimate the amounts of N-nitroso derivatives formed in vivo from the precursors. The nitrosation rate for PZ was 50%-70%, compared with 1%-3% for MOR. The results are compared with those of long-term carcinogenesis studies with sodium nitrite plus amines. (58 refs.)

**78-0165 Liposolubility as an Aspect of Nitrosamine Carcinogenicity: Quantitative Correlations and Qualitative Observations.** (Eng) Singer, G. M. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Taylor, H. W.; Lijinsky, W. *Chem Biol Interact* 19(2): 133-142; 1977.

The biological activities of several carcinogenic nitrosamines in male and female Sprague-Dawley rats were examined in relation to their relative liposolubilities [measured as their partition coefficients (P) between water and n-octyl alcohol]. There was no significant difference between the findings for either sex. Two correlations between P and carcinogenicity were found for cyclic nitrosamines: a linear correlation with animals bearing olfactory carcinomas induced by substituted N-nitrosopiperidines (except for N-nitroso-2-methylpiperidine), and a parabolic correlation with the relative mean lifetime of animals with hepatocellular carcinomas induced by cyclic nitrosamines. There was no apparent correlation for squamous cell carcinomas of the upper gastrointestinal tract induced by related cyclic nitrosamines. The effect of liposolubility on the carcinogenicity of noncyclic nitrosamines was less evident. N-Nitroso-di-n-butylamine and N-Nitroso-di-n-methyl-n-dodecylamine, which induce bladder carcinoma in rats, had high partition coefficients. (22 refs.)

**78-0166 Nitrites, Nitrosamines, and Meat.** (Eng) Engel, R. E. (Meat and Poultry Inspection Program,



Food Safety and Quality Service, US Dept. Agriculture, Washington, DC 20250). *J Am Vet Med Assoc* 171(11): 1157-1160; 1977.

Although nitrite in meat products can combine with amines to form carcinogenic nitrosamines, nitrite also provides the necessary protection against botulism. Therefore, the Department of Agriculture is permitting its continued use at low levels pending the development of a safe substitute. (16 refs.)

**78-0167 Bacterial Flora and Nitrite Production in the Stomach after Gastroenterostomy. Experimental Aspects of the Pathogenesis of Carcinoma in the Operated Stomach.** (Ger) Schlag, P. (Abteilung für Allgemeine Chirurgie, Universität Ulm, Steinhövelstrasse 9, D-7900 Ulm, W. Germany); Wonka, W.; Meyer, H.; Feyerabend, G.; Merkle, P. *Langenbecks Arch Chir* 344(2): 109-114; 1977.

The effects of gastroenterostomy (GEO) on nitrite production in the stomach were investigated in male SPF-Wistar rats subjected to either GEO, GEO without enteroanastomosis, or GEO according to the Roux procedure. Rats undergoing GEO without enteroanastomosis had an enhanced amount of nitrite-producing bacteria in the stomach. This increases the nitrite concentration in the gastric fluid, which could bring about an increased production of nitrosamines which are carcinogenic. These changes can be prevented by a Roux-Y-gastroenterostomy, a fact that should be considered during reconstruction of the alimentary tract following gastric surgery. (11 refs.)

**78-0168 Sequential Alteration of the Pancreas During Carcinogenesis in Syrian Hamsters by N-Nitrosobis(2-oxopropyl)amine.** (Eng) Takahashi, M. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB 68105); Pour, P.; Althoff, J.; Donnelly, T. *Cancer Res* 37(12): 4602-4607; 1977.

N-Nitrosobis(2-oxopropyl)amine-induced alterations in the Syrian hamster pancreas were examined sequentially in animals given weekly sc injections of the carcinogen (10 mg/kg) for 5, 7, or 9 wk and sacrificed at 2-wk intervals after the last injection. The results indicate that the ductular cells (cells of intercalated or intralobular ductules and especially, those of peri- and intralobular ductules) were the most responsive. The initial proliferation (multiplication) and distension of the ductules seemed due to primary hyperplasia of the ductular cells, followed by metaplasia, atypia, and malignant alteration. Among 75 induced adenocarcinomas, most were of ductal origin; only a few seemed to arise from the ductal epithelium (interlobular, secondary, and main ducts). There was no preferential segment for tumor development. However, about one-third of the adenocarcinomas in the head of the pancreas had a periampullary location, and most neoplasms in other pancreatic lobes arose along the main pancreatic ducts. There was evidence of leaking of the pancreatic juice

through altered epithelium of the main ducts, and this may have caused a marked periductal chronic inflammatory reaction. (11 refs.)

**78-0169 Local and Systemic Effects of 1-Acetoxypropylpropylnitrosamine in Syrian Golden Hamsters.** (Eng) Althoff, J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105); Grandjean, C.; Pour, P.; Gold, B. *Z Krebsforsch* 90(2): 127-140; 1977.

The acute and chronic effects of 1-acetoxypropylpropylnitrosamine (APPN) were investigated in Syrian hamsters. In the acute study, a single dose of 250, 500, 1,000, or 2,000 mg/kg was injected sc. The LD<sub>50</sub> was 500 mg/kg (females: 707 mg/kg; males: 354 mg/kg). During the chronic study, the hamsters received 50, 25, 12.5, or 0 mg/kg APPN sc once weekly for life. Av life span, tumor latency, and multiplicity of neoplasms were dose-dependent. Small sc nodules could be palpated at the injection site after 15 wk of treatment. Most of the tumors were mesenchymal or epithelial in origin, and they were highly invasive; epithelial tumors were also induced in remote organs (mainly lymph nodes and lungs). Sc tissue exhibited a plateau response to the carcinogen. The anterior portion of the nasal cavities developed papillary polyps, squamous cell papillomas, and epidermoid carcinomas with and without keratinization; adenocarcinomas developed in the middle and posterior portions of the nasal cavities. The malignant tumors invaded the surrounding tissue. Tumor frequency and multiplicity showed a positive dose-response relationship for the respiratory tract and its segments. Females were affected more than males. The digestive and genital tract neoplasms of females (papillomas and epidermoid carcinomas) may have been related to the systemic effects of APPN. Thus, not all dialkyl-nitrosamine produce cancer exclusively in remote organs, as was previously suggested. (23 refs.)

**78-0170 Comparison of the Effect of  $\beta$ -oxidized Dipropylnitrosamine Metabolites Administered at Equimolar Doses to Syrian Hamsters.** (Eng) Althoff, J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105); Grandjean, C.; Pour, P.; Bertram, B. *Z Krebsforsch* 90(2): 141-148; 1977.

The carcinogenic effect of equimolar doses of dipropylnitrosamine (DPN) and its  $\beta$ -oxidized metabolites on Syrian hamsters was determined. The animals received weekly sc injections of 6.5 mg DPN, 7.3 mg 2-hydroxypropylpropylnitrosamine (HPPN), 7.2 mg 2-oxopropylpropylnitrosamine (OPPN), 5.2 mg methylpropyl-nitrosamine (MPN), 8.1 mg N-nitrobis(2-hydroxypropyl)nitrosamine (BHPN), or 7.9 mg 2,2'-dimethyldipropylnitrosamine (DMDPN). Tumor incidence in the respiratory and digestive tracts with DPN was 100%



and 7%; the respective incidences for the other compounds were as follows: HPPN 87% and 10%, OPPN 100% and 47%, MPN 97% and 90%, BHPN 80% and 70%, and DMDPN 7% and 3%. OPPN and BHPN induced a large percentage of tumors in both the urogenital and vascular systems, but MPN induced tumors only in the vascular system. In the respiratory tract, the segmental tumor distribution and histological types varied according to the compounds. These findings do not support the idea that the  $\beta$ -oxidized metabolites of DPN are the proximate carcinogens of the parent compound. (20 refs.)

**78-0171 Transplacental Effect of Nitrosamines in Syrian Hamsters. IV. Metabolites of Dipropyl- and Dibutylnitrosamine.** (Eng) Althoff, J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105); Grandjean, C.; Pour, P. *Z Krebsforsch* 90(2): 119-126; 1977.

The occurrence of transplacental carcinogenesis in Syrian golden hamsters exposed during gestation to dipropyl- and dibutylnitrosamine derivatives was examined. Pregnant females were given a single sc injection of 100 mg/kg 2-hydroxypropylpropylnitrosamine (HPPN), 2-oxopropylpropylnitrosamine (OPPN), methylpropylnitrosamine (MPN), N-nitrobis(2-hydroxypropyl)nitrosamine (BHP), or 4-hydroxybutylbutylnitrosamine (HBBN) on days 8, 10, 12, or 14 of gestation. All nitrosamines were detected unchanged in both the maternal and fetal tissues 15 min after injection, and they were still present after 4 to 6 hr. Nitrosamine levels in the fetus approximated those of the maternal blood after HPPN treatment; fetal values were approx half those of maternal blood for the other treatment groups. The overall incidence of transplacentally induced tumors was lower in the F<sub>1</sub> generation than in their mothers, and the former demonstrated comparatively longer latent periods. Respiratory tract neoplasms were detected in HPPN-, OPPN-, MPN-, and BHP-treated animals; digestive tract neoplasms were detected in all treated animals and offspring; and endocrine neoplasms were detected in all animals except mothers treated with MPN. The transplacental carcinogenic effect was greatest at day 14 of gestation. Neoplasms originating in other organs were not associated with the transplacental effect of these nitrosamines. (20 refs.)

**78-0172 Cell Kinetics of Mouse Urinary Bladder Epithelium. IV. Changes in Cell Proliferation, Nuclear DNA Content, and Number of Diploid, Tetraploid and Octoploid Cells after a Single Dose of Dibutylnitrosamine.** (Eng) Farsund, T. (Haukeland Sykehus, 5016 Bergen, Norway). *Virchows Arch [Cell Pathol]* 25(3): 179-189; 1977.

The susceptibility of the urinary bladder epithelium of hairless male mice (hr/hr Oslo strain) to the immediate cell-injurious effect of dibutylnitrosamine (DBN) was evaluated, and the regenerative response after injury was studied and

compared with the pattern seen after the administration of cyclophosphamide (CP). A single dose of 0.01 ml DBN was injected sc into the mice, and the animals were sacrificed up to 336 hr after they were inoculated. The mitotic rate was 0.02 mitosis/hr at 24 hr, 0.06 at 48 hr, and 0.63 at 96 hr; thereafter, no mitotic activity was observed. From 0 to 6 hr, DNA synthesis in the diploid cells was blocked; the number of tetraploid and octoploid cells remained almost normal, but the proportion of diploid cells was slightly diminished. From 6 to 18 hr, the initial block was released, and the diploid cells then proceeded rapidly through S and on to G<sub>2</sub>. Later, at 36-42 hr and at 44-46 hr, two more regenerative waves of DNA synthesis occurred among the diploid cells. All three periods of increased DNA synthesis in the diploid cells were not accompanied by similar waves of increased DNA synthesis in the tetraploid cells. The mechanism of repeated DNA cycling was thereby permanently injured, but the cells were viable. No octoploid cell hyperplasia was found, but there were three periods of very few octoploid cells: at 12-24 hr, 40-46 hr, and 96-168 hr. Total cell number was not affected. DBN thus primarily affects the diploid basal cells in their S phase, presumably via the bloodstream. Qualitatively, the injury provoked by DBN is very different from that caused by CP, but whether this has anything to do with the carcinogenicity of DBN is not known. (21 refs.)

**78-0173 Kinetics of Formation of O<sup>6</sup>-Ethylguanine in, and Its Removal from Liver DNA of Rats Receiving Diethylnitrosamine.** (Eng) Scherer, E. (Div. Chemical Carcinogenesis, Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., 108, Sarphatistraat, Amsterdam, Netherlands); Steward, A. P.; Emmelot, P. *Chem Biol Interact* 19(1): 1-11; 1977.

O<sup>6</sup>-Ethylguanine (EG) formation in the female Sprague-Dawley rat liver was investigated following administration of a single dose of diethylnitrosamine (DENA or <sup>14</sup>C-DENA): the relatively nontoxic doses 0.5, 2, and 10 mg/kg and the toxic dose 134 mg/kg were given by stomach tube in 5 ml water/kg. The dose response for 7-ethylguanine (7-EG), 3-ethylguanine, the pyrimidine oligonucleotide fraction containing ethylphosphotriesters and fraction X was linear, but the amount of EG showed a larger increase with dose. The EG/7-EG ratio increased with increasing dose. Removal of EG from the liver was constant following doses of 0.5, 2, and 10 mg/kg DENA (half life, 3-4 yr); however, 50 mg/kg DENA strongly decreased the disappearance rate of EG formed by 2 mg/kg <sup>14</sup>C-DENA. Thus, EG formation was facilitated by some dose-dependent process or condition. Support for this view was obtained by the markedly enhanced <sup>14</sup>C-EG content of DNA following pretreatment of the rats with nonradioactive DENA, which was allowed to be metabolized completely prior to administration of a tracer dose of <sup>14</sup>C-DENA. Pretreatment had no effect on other ethylation products or on the half life of <sup>14</sup>C-EG. Experiments in which the rats were pretreated with 10 mg/kg DENA and given 2 mg/kg <sup>14</sup>C-DENA at 0, 2, 4, 6, 9, 12, and 24 hr indicated



that pretreatment created not only an early enhancing condition, but also a late and stable inhibitory condition. The possible role of EG in hepatocarcinogenesis is discussed. (23 refs.)

- 78-0174 In Vivo Repair of Rat Liver DNA Damaged by Dimethylnitrosamine or Diethylnitrosamine.** (Eng) den Engelse, L. (Chemical Carcinogenesis Div., Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Philippus, E. J. *Chem Biol Interact* 19(1): 111-124; 1977.

The effects of dimethylnitrosamine (DMN: 1.0 or 10 mg/kg ip) and diethylnitrosamine (DEN: 13.4 mg/kg ip) on the sedimentation pattern of female Sprague-Dawley rat liver DNA was studied with regard to time and dose dependence. Doses of 10 mg/kg DMN and 13.4 and 134 mg/kg DEN decreased the sedimentation rates markedly 24 hr after injection, but 1 mg/kg DMN decreased it only slightly. The higher dose of DMN was as effective as the higher dose of DEN, suggesting that the number of single-strand breaks after lysing is not significantly different for the two groups. After all treatments, the repair of single-strand breaks resulted in a shift toward control sedimentation patterns. Damage induced by DEN was repaired at a substantially lower rate than DMN-induced damage between days 1 and 14. Preliminary experiments with the highest doses of these compounds indicated that DMN damage was repaired to a more appreciable extent than DEN damage between days 14 and 28. Both nitrosamines resulted in about the same amount of total alkylation and alkylation at the O<sup>6</sup> of guanine. At 24 hr, alkylation at the N<sup>3</sup> of adenine was about twofold higher with DEN; sixfold higher amounts of 7-alkylguanine were noted with DMN. From days 1 to 14, the half-life values for 7-methylguanine and 7-ethylguanine were 86 and 72 hr, respectively. These results are discussed in relation to the possible significance of DNA alkylation and repair in the formation of (pre)cancerous lesions in the liver. (35 refs.)

- 78-0175 Radioactive Components in the Acid-soluble Fraction of Mouse Liver Cytosol after Dimethylnitrosamine[Methyl-<sup>14</sup>C] Administration.** (Eng) Daugherty, J. P. (Lab. Molecular Biology, Univ. Alabama Medical Center, Birmingham, AL 35294); Clapp, N. K.; Zehfus, M. H.; Brock, S. E. *Gann* 68(5): 697-701; 1977.

The in vivo metabolites derived from radioactively labeled dimethylnitrosamine (DMN) were examined by the use of the column chromatography (CC) in which the columns were calibrated with known in vitro DMN metabolites. Acid-soluble components of mouse liver cytosol were prepared at time intervals after male RFM mice were administered a single carcinogenic dose of <sup>14</sup>C-DMN (10 mg/kg ig; 2  $\mu$ Ci/animal) and separated by CC. The cytosol elution profiles could be resolved into numerous regions. Several corresponded to the elution peaks of the in vitro DMN metabolites, but other peaks were also evident. The results suggest that the

DMN metabolites produced by rat liver microsomes in vitro (formaldehyde, formic acid, methylamine, N-methylhydrazine, N-methylhydroxylamine, and N,N-dimethylhydrazine) are also produced in the mouse liver *in vivo*. However, numerous other radioactive compounds are present that may or may not represent direct decomposition products of DMN. The significance of these metabolites to the pathogenicity of DMN is not known. (29 refs.)

- 78-0176 Effect of Precursors of Endogenous Dimethylnitrosamine on Its Dimethylase Activity in Rat Liver.** (Rus) Karpilovskaya, E. D. (Scientific Res. Inst. Nutrition Hygiene, Kiev, USSR); Rubenchik, B. L. *Biull Eks Biol Med* 84(12): 717-719; 1977.

The effect of dimethylamine (DMA) and/or sodium nitrite (SN), on the activity of endogenous dimethylnitrosamine (DMNA) dimethylase (DMase) was studied in male rats (strain unspecified). Two series of experiments were carried out. In the first series animals received a single po administration of DMA (150 mg/kg), SN (125 mg/kg), DMA + SN (150 mg/kg), or DMNA (15 mg/kg). The mice were divided into two groups: Group 1 received chemicals alone, Group 2 was given the DMase inductor casein (5 g, po) 1 day prior to administration of the chemicals. In the second series, rats received repeated daily administration of DMA (150 mg/kg), SN (3 mg/kg), DMA + SN, above, or DMNA (6 mg/kg). Ninety-two hours after administration, of the compounds in the first series and 3.2 mo after the start of the second experiment rats were sacrificed and the DMase activity in the liver microsomes was assessed. Administration of DMNA precursor and DMNA in both series of experiments resulted in an elevation of DMase activity. The increase of DMase activity was more pronounced after casein administration. To verify the hypothesis that DMA itself is a DMase inductor, rats were given actinomycin D (1.5 g/kg, ip, 1 hr prior to DMA administration). Administration of the antibiotic prevented the DMA-induced increase of DMase activity. (9 refs.)

- 78-0177 Statistical Aspects of Extrapolation of Dichotomous Dose-Response Data.** (Eng) Brown, C. (Biometry Branch, NCI, NIH, Public Health Service, US Dept. Health, Education, and Welfare, Bethesda, MD 20014). *J Natl Cancer Inst* 60(1): 101-108; 1978.

A mathematical model based on the multistage hypothesis of carcinogenesis is presented in which exposure of C3H mice to diethylstilbestrol (mammary carcinoma) and exposure of female white rats to dimethylnitrosamine (liver carcinoma) are used as examples. The model extrapolates the results of bioassay experiments performed at high dose levels to the carcinogenic risk at lower dose levels. Although this model is not the final solution to the problem of dose extrapolation it does represent a reasonable physiologic model for carcinogenesis with considerable flexibility and generality. (23 refs.)



**78-0178 Rat Hepatocyte Primary Cell Culture-mediated Mutagenesis of Adult Rat Liver Epithelial Cells by Procarcinogens.** (Eng) San, R. H. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Williams, G. M. *Proc Soc Exp Biol Med* 156(3): 534-538; 1977.

Rat hepatocyte primary cell (HPC) cultures were used as feeder systems to study carcinogen-induced mutations in adult Wistar rat liver (ARL) epithelial cells. A mixture of  $5.4 \times 10^6$  hepatocytes was mixed with  $2.4 \times 10^6$  ARL cells and exposed to either  $10^{-7}$  M 7,12-dimethylbenz(a)anthracene,  $10^{-3}$  M dimethylnitrosamine (DMN), or  $10^{-5}$  M 2-acetylaminofluorene (AAF) in dimethyl sulfoxide (DMSO). Treatment of HPC + line ARL 6 cells with DMBA resulted in 2.3 times the number of mutations observed in ARL 6 cells alone. Similar treatment of cells with DMN and AAF resulted in increases of 2.4 and 1.5 times the untreated value, respectively. Treatment of the cells with DMSO resulted in no appreciable increase. Repetition of the experiments with line ARL 16 increased mutant incidence 1.5 times with DMBA, 1.9 times with DMN, and 3.2 times with AAF; the respective figures for ARL 11 cells were 2.9, 2.1, and 3.0. Thus, HPC cultures can be used as feeder systems for enhancing mutagenesis by procarcinogens requiring metabolic activation in established lines of ARL cells. (16 refs.)

**78-0179 Basement Membrane Changes under Neoplastic Oral Mucous Membrane. Ultrastructural Observations, Review of the Literature, and a Unifying Concept.** (Eng) McKinney, R. V. (Dept. Oral Pathology, Sch. Dentistry, Medical Coll. Georgia, Augusta, GA 30902); Singh, B. B. *Oral Surg* 44(6): 875-888; 1977.

Basement membrane changes in the cheek pouch of Syrian golden hamsters were examined following applications of 7,12-dimethylbenz(a)anthracene (DMBA: 0.25-0.50 ml, 3 times/wk for 12 wk) via a tuberculin plastic syringe. Following DMBA application, there was a duplication and triplication of the basement membrane, a more flocculent appearance of the lamina densa and a wider lamina lucida. There was also an occasional break in the membrane under advanced dysplastic epithelium. Exocytosis of WBC into the intercellular space between dysplastic basal cells was observed. The basal cells from the carcinoma in situ lesions demonstrated cytoplasmic projections of variable lengths. The basement membrane under these projections was generally continuous; however, there were focal breaks usually adjacent to the epithelial intercellular spaces. Many specimens had fewer collagen fibers in the lucent areas near these discontinuities. Squamous cell carcinoma lesions had epithelial projections occasionally surrounded by a complete basement membrane. There were breaks in the membrane in the region of the intercellular spaces. Based on these results and a review of the literature, it is suggested that neoplastic epithelial cells release a collagenolytic enzyme into the intercellular spaces. This enzyme permeates the basement membrane, causing breaks and focal loss of stroma contiguous with the intercel-

lular spaces. Neoplastic cells then develop pseudopodia that eventually extend through the breaks in the membrane. Changes in the basement membrane may indicate the progression of carcinoma in situ to invasive carcinoma. (88 refs.)

**78-0180 Absence of Mutagenicity of Coralyne and Related Antileukemic Agents: Structural Comparison with the Potent Carcinogen 7,12-Dimethylbenz(a)anthracene.** (Eng) Cheng, C. C. (Midwest Res. Inst., Kansas City, MO 64110); Engle, R. R.; Hodgson, J. R.; Ing, R. B.; Wood, H. B.; Yan, S. J.; Zee-Cheng, R. K. *J Pharm Sci* 66(12): 1781-1783; 1977.

Because of the structural similarity between the antileukemic alkaloid coralyne and the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) and between the antileukemic alkaloid nitidine and the carcinogen 5-methylchrysene, coralyne sulfoacetate, nitidine chloride, homocoralyne sulfopropionate, nitidine methosulfate, and the tetramethoxy analog of nitidine were tested for mutagenicity against the histidine-auxotroph strains of *Salmonella typhimurium* TA1537, TA1538, TA98, and TA100. DMBA was used as a reference standard. The mutagenicity of the antileukemic compounds was completely eliminated or drastically reduced, but the mutagenic response was generally high for DMBA. The results suggest that the presence of a quaternary nitrogen atom and alkoxy groups could be important in alleviating the mutagenicity of the parent mutagenic and carcinogenic hydrocarbons. (55 refs.)

**78-0181 The Influence of Dietary Yeast Grown on n-Paraffins on Mammary Tumours Induced by 7,12-Dimethylbenzanthracene and 3-Methylcholanthrene in Rats.** (Eng) Guaitani, A. (Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea, 62-20157 Milan, Italy); Morasca, L.; Balconi, G.; Bartosek, I.; Garattini, S.; Paglialonga, S. *Toxicol Lett* 1(3): 157-168; 1977.

Dietary levels of yeast grown on n-paraffins (single-cell proteins, SCP) were given for 7 mo to 1-mo-old female CD-COBS rats treated at age 2 mo with a single po dose of 7,12-dimethylbenzanthracene standard or 3-methylcholanthrene (3-MC: 26.6 mg/rat). A control group received the same dietary levels of SCP and a single po dose of olive oil. The same carcinogen/olive oil treatments were given to rats fed a standard, non-SCP diet. Growth rates and food consumption were not altered in SCP-fed rats compared with rats receiving a standard diet. The leukopenia observed after DMBA administration was not changed by the SCP diets. In the DMBA experiments, tumors appeared at the same time in animals fed the standard and SCP diets. In the MC study, the SCP-diet groups had a tumor-free life of 60 days compared with 30 days for the group on the (DMBA: 2.5 or 10.0 mg/rat) diet. The incidence of mammary tumors induced by polycyclic hydrocarbons was not modified by SCP. These results suggest that dietary SCP does not influence chemical carcinogenesis in rats. (28 refs.)



**78-0182 Effect of Dimethylbenzanthracene (DMBA) on the Pituitary-Adrenal Axis of the Rat.** (Fre.) Heuson-Steinon, J. A. (Laboratoire d'Histologie de la Faculté de Médecine, Bordet, 1000 Brussels, Belgium); Danguy, A.; Toubreau, G.; Heuson, J.C.; Pasteels, J. L. *Biol Cellulaire* 30(1): 11a; 1977. (no refs.)

**78-0183 Multiple Autotransplantation of Rat Mammary Tumors Induced by 7,12-Dimethylbenz(a)anthracene: Brief Communication.** (Eng) Lee, C. (Dept. Urology, Northwestern Univ. Medical Sch., 303 E. Chicago Ave., Chicago, IL 60611); Shih, A.; Oyasu, R. *J Natl Cancer Inst* 60(2): 473-476; 1978.

To minimize the effects of the tissue trauma and infection that can be introduced during serial sampling of tissues, mammary tumors induced in Sprague-Dawley rats by 7,12-dimethylbenz(a)anthracene were excised, cut into 1- and 2-mm<sup>3</sup> pieces, and autotransplanted sc along the mammary line at six sites. Of 48 rats that received tumor autografts, 32 developed actively growing tumors. The growth pattern of the grafts appeared uniform in each animal, and 20-30 days were required for the grafts to reach 2 cm in diameter. The tumors were identified as moderately well-differentiated adenocarcinomas. In the remaining 16 rats, the grafts did not grow. Histologic examination showed that they appeared viable, but dormant. Tumor development in each host seemed to be an all-or-none phenomenon: all six transplantation sites were actively growing in the 32 animals with active grafts. Tumors derived from autotransplantation were identical to their primary tumors with respect to histologic features, hormone dependency, content of estrogen receptors, and ability to incorporate <sup>3</sup>H-leucine. In addition, the autotransplanted tumors derived from a single primary varied little with regard to these parameters. Multiple autotransplantation provides an opportunity for serial sampling individual tumors for repeated morphologic and biological evaluations. (13 refs.)

**78-0184 Structure of 7,12-Dimethylbenz(a)anthracene 5,6-Oxide Derivatives Linked to the Ribose Moiety of Guanosine (Letter to Editor).** (Eng) Kasai, H. (Dept. Chemistry, Columbia Univ., New York, NY 10027); Nakanishi, K.; Frenkel, K.; Grunberger, D. *J Am Chem Soc* 99(26): 8500-8502; 1977.

The preparation of guanosine-dimethylbenz(a)anthracene 5,6-oxide adducts that coincide with rat liver tissue-culture products is reported. Data on the circular dichroism and the UV and nuclear magnetic resonance spectra of the adducts are presented. (12 refs.)

**78-0185 Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits.** (Eng) Stenback, F. (Dept. Pa-

thology, Univ. Oulu, Oulu, Finland). *Acta Pharmacol Toxicol* 41(5): 417-431; 1977.

Several externally used chemicals were applied repeatedly to the skin of Swiss mice and New Zealand rabbits. These chemicals included 4-hydroxyanisole, benzalkonium chloride, bromodeoxyuridine, iododeoxyuridine, 5-nitroacenaphthene, N-N-diethyltoluamide, hexachlorophene, p-aminobenzoic acid, benzophenone, isopropyl myristate, pyrogallol, resorcinol and ethylhexanediol. Also tested were a commercial hairspray, a dandruff shampoo, and an antidandruff agent. Local and systemic changes were studied and the tumor incidence was compared with that induced by the carcinogen 9,10-dimethylbenz(a)anthracene. The mice showed no local toxic changes or tumor formation, and the systemic tumor incidence, ie, tumors of the liver, lungs, lymphatic system, and other organs, was similar to that of control animals. In rabbits, proliferative, benign, and malignant ear tumors were observed in the positive controls, thereby demonstrating the efficiency of this model. Local toxic changes were seen in benzalkonium- and hexachlorophene-treated animals, but no skin tumors developed. Four animals had uterine tumors. (33 refs.)

**78-0186 Pancreatic Carcinoma in Rats Induced by 7,12-Dimethylbenzanthracene.** (Eng) Umeyama, K. (First Dept. Surgery, Osaka City Univ. Medical Sch., Osaka, Japan); Satake, K.; Yamashita, K.; Yamamoto, S.; Kamino, K.; Sowa, M. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 385-396; 1977.

The development of pancreatic carcinoma was studied in male Sprague-Dawley rats given 1 mg of 7,12-dimethylbenz(a)anthracene (DMBA) in the body of the pancreas by a double-lumen needle. All 55 rats survived at least 120 days; 8 died between days 153 and 251, and 47 were sacrificed between days 120 and 274. Pancreatic carcinoma was found in 33 rats; 14 rats had ductal proliferation, 4 had fibrosarcoma, and 4 did not develop any abnormalities. Of the 33 rats with malignant tumors, 12 had tubular adenocarcinoma, 19 had poorly differentiated adenocarcinoma, and 2 had acinar cell carcinoma. Of the 12 rats with tubular adenocarcinoma, there was invasion of the liver (1), spleen (3), stomach (1), and intestine (1). Of the 19 rats with poorly differentiated adenocarcinoma, invasion occurred in the liver (3), spleen (8), stomach (3), intestine (3), and kidney, omentum, lymph node, or mesentery (10). Since the tumors had a close morphological resemblance to human pancreatic adenocarcinoma and since they were not found in other organs, this model may be a good one for study of the disease process in humans. (23 refs.)

**78-0187 Bioactivation of Procarcinogens to Mutagens in Human Fetal and Placental Tissues.** (Eng)



Jones, A. H. (Dept. Pharmacology, Univ. Washington Sch. Medicine, Seattle, WA 98195); Fantel, A. G.; Kocan, R. A.; Juchau, M. R. *Life Sci* 21(12): 1831-1835; 1977.

The ability of human fetal S-9 fractions of liver, adrenal, kidney, lung, spleen, pancreas, and ovary tissue and the microsomal fraction from placentas to activate benzo(a)pyrene (BP), 7,12-dimethylbenz(a)anthracene (DMBA), and N-2-fluorenylacetamide (FAA) to intermediate metabolites that produce mutations in *Salmonella typhimurium* was examined. Fetal ovary, spleen and pancreas showed negative results for all promutagens. Fetal liver had the highest consistency of conversion, particularly of FAA. Tissues from very early stages of gestation had low or negligible activity. In comparison to hepatic tissue, placental tissue was unable to catalyze conversion of FAA to mutagens in spite of a high capacity to bioactivate BP or DMBA. Kidney and lung tissue had positive conversion results and low aryl hydrocarbon hydroxylase (AHH) activity. In spite of high AHH activity, the fetal adrenal was relatively inactive in this activation. (18 refs.)

**78-0188 Mutagenicity of Diallylate, Sulfallate, and Triallate and Relationship Between Structure and Mutagenic Effects of Carbamates Used Widely in Agriculture.** (Eng) de Lorenzo, F. (Il Cattedra di Chimica Biologica, Il Facolta di Medicina e Chirurgia, Univ. Naples, Via Sergio Pansini, 5, 80131, Naples, Italy); Staiano, N.; Silengo, L.; Cortese, R. *Cancer Res* 38(1): 13-15; 1978.

The mutagenicity of 20 carbamates used as herbicides and fungicides was investigated using the Ames mutagenicity test with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100. In the presence of the S-9 microsomal fraction from Sprague-Dawley rat liver homogenates, diallate (S-2,3-dichloroallyl diisopropylthiocarbamate), sulfallate (2-chloroallyl diethylthiocarbamate), and triallate (S-2,2,3-trichloroallyl diisopropylthiocarbamate) were mutagenic for strains TA1535 and TA100, which indicated that the compounds cause base-pair substitution mutations. The number of revertants per nanomole induced by the three mutagens was 8, 2.2, and 1.5, respectively. The 2-chloroallyl group common to all three may be responsible for their mutagenicity: the 17 compounds without this group were not mutagenic. Since diallate has been shown to be carcinogenic in mice, these findings substantiate the association between mutagenicity and carcinogenicity. (18 refs.)

**78-0189 Influence of Phenobarbital on Microspherule Production by Urethan in Mouse Hepatocyte Nucleoli.** (Eng) Lombardi, L. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milan, Italy). *Cancer Res* 37(12): 4378-4381; 1977.

Four-day-old C3Hf mice received one daily ip injection of phenobarbital (30 mg/kg) in 0.9% NaCl solution of vehicle

alone for 3 days. On the fourth day the mice were treated with a single ip injection of urethan (1 mg/g) in 0.9% NaCl solution or vehicle alone. The mice were killed 10 hr after the last injection, and their liver tissue was studied by electron microscopy. Aggregates of an essentially proteinaceous fibrillar material were observed in the hepatocyte nucleoli of the control mice treated with 0.9% NaCl solution. After treatment with phenobarbital alone, which induced the typical proliferation of hepatocyte smooth endoplasmic reticulum, the mean number of fibrillar aggregates per nucleolus was 19% lower than that of the controls. After treatment with urethan alone, microspherules that were somewhat larger and denser than control fibrillar aggregates were observed. The mean number of microspherules plus fibrillar aggregates per nucleolus was 91% higher than the mean number of control fibrillar aggregates. When phenobarbital treatment was followed by urethan treatment, the mean number of microspherules plus fibrillar aggregates per nucleolus was 36% lower than that after treatment with urethan alone. This inhibition of urethan action is probably related to drug-metabolizing enzyme induction by phenobarbital. (19 refs.)

**78-0190 Transplacental Lung Tumorigenesis in the Athymic Mouse.** (Eng) Anderson, L. M. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Budinger, J. M.; Maronpot, R. R.; Good, R. A. *Cancer Res* 38(1): 137-141; 1978.

The incidence and histological characteristics of lung tumors induced by a single transplacental exposure to urethan were investigated in athymic nude (nu/nu) mice and normal littermates. Female BALB/c nu/+ mice, pregnant by nu/+ males, were given injections of urethan on day 17 (1.0 mg/g) or day 19 (0.1, 0.5, or 1.0 mg/g) of gestation. After 16 wk, the incidence of primary lung tumors was similar in nude and normal offspring treated with carcinogen on either day, with a higher incidence after treatment on day 19. Histologically, the nu/nu tumors differed from normal in the appearance of many atypical basophilic cells and in a tendency to invade both the parenchyma and the pleural surface. It is concluded that the absence of a thymus does not affect the incidence of transplacentally induced primary lung tumors or alter the known perinatal increase in sensitivity. The histological findings suggest progression of the nu/nu lung adenomas to a more atypical, invasive form than those seen in the normal mice, indicating a progression that may have occurred prematurely in the absence of a thymus-dependent immune response. (18 refs.)

**78-0191 Carcinogenicity of Urethane. II. The Role of Age and Treatment Schedule in the Carcinogenic Action of Urethane.** (Hun) Bojan, F. (Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudományi Egyetem, Debrecen, Hungary). *Magy Onkol* 21(4): 239-246; 1977.



The carcinogenic effect of urethane (U), was studied in CFLP mice as a function of age and treatment schedule. There was no significant difference in terms of lung tumor induction rates (TIR) 5 wk after ip and po administration of U to adult mice (70% for 1 mg/kg ip, 63% for 1 mg/kg po; 90% for 2 mg/kg ip, 93% for 2 mg/kg po). The carcinogenic effect of U excreted in milk was studied in another experiment in which lactating mothers were treated with 4 x 0.5 mg/kg U ip or po on 4 consecutive days. The suckling mice were aged 1-4 days (Group 1) or 12-16 days (Group 2). They were autopsied 5 wk after treatment of the mothers was initiated. The TIR were 10% for males and 16% for females in Group 1, 4% for males and 5% for females in Group 2. The transplacental carcinogenic effect of U was studied in young rats that were sacrificed 35 days after the administration of a single 1-mg/kg dose to the mothers during pregnancy. No tumors were found in mice whose mothers were treated on gestation days 10 and 11, but TIR were 3%-4% if treatment occurred on day 12, and 32% (males) and 41% (females) if treatment occurred on day 19. The 1-day to 3-mo-old offspring of untreated mothers were given a single 1-mg/kg dose of U ip and sacrificed 5 wk later to study the effect of age on carcinogenesis. The TIR were 74%-80% for 1-day-old mice, 72%-75% for 2-wk-old mice, 69%-70% for 1-mo-old mice, and 65%-70% for 3-mo-old mice. However, the number of tumors per animal was considerably higher among young mice (2.16-2.35 in mice treated at age 1 day vs 1.15-1.40 in mice treated at age 90 days). The findings indicate the considerable influence of the age of the animals and treatment schedule on the carcinogenicity of U in CFLP mice. (24 refs.)

**78-0192 Bioassay of Lindane for Possible Carcinogenicity.** (Eng) Fredrickson, D. S. (NIH, Bethesda, MD 20014). *Fed Regist* 42(218): 58791; 1977.

Male Osborn-Mendel rats and B6C3F1 mice were exposed to 236 or 472 ppm lindane for 80 wk; female animals, to 135 or 270 ppm for 80 wk. No significant tumor incidence was noted in the rats. The low incidence of hepatocellular carcinomas in male mice, even at high doses, was not significant. It was concluded that lindane is not carcinogenic in these animals at these doses. (no refs.)

**78-0193 Epidermal Intercellular Relationships During Carcinogenesis and Cocarcinogenesis as Revealed by Scanning Electron Microscopy.** (Eng) Komitowski, D. (Inst. Experimental Pathology, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany); Goerttler, K.; Lohrke, H. *Virchows, Arch [Cell Pathol]* 24(4): 317-333; 1977.

Scanning electron microscopy (SEM) investigations were carried out on the skin of 80 NMRI mice treated with the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA: 0.1  $\mu$ M) or the cocarcinogen 12-O-tetradecanoylphorbol-13-acetate

(TPA: 0.1  $\mu$ M). The results were correlated with histologic, transmission electron microscopic, and autoradiographic observations. The epidermis of TPA-treated animals was markedly hyperplastic, with an orderly arrangement of cell layers. Autoradiographically, only the basal cells were heavily labeled. SEM and transmission electron microscopy revealed a decrease in intercellular connections and a dilatation of the intercellular spaces. After DMBA treatment, the epidermis was moderately hyperplastic but severely dysplastic with <sup>3</sup>H-thymidine-labeled cells in the upper layers. The most characteristic findings were the loss of the intercellular connections, especially the lateral ones, and a pronounced dilatation of the intercellular spaces. The SEM results were quantified morphometrically. (52 refs.)

**78-0194 Induction of the Deficient Acid DNase Activity in Mouse Interfollicular Epidermis by Croton Oil as a Possible Tumor Promoting Mechanism.** (Eng) Tupper, H. S. (Dept. General Pathology and Neuropathology, Univ. Louvain, Box 5260, Ave. Emmanuel Mounier 52, B-1200 Bruxelles, Belgium). *Z Krebsforsch* 90(2): 197-210; 1977.

The histochemical activity of acid DNase, intensity of nucleic acid staining, and histological alterations in male NMRI mouse interfollicular epidermis (IFE) were investigated after a single dose (0.1 ml of 0.5% acetone soln) of either croton oil or podophyllin. Podophyllin induced intense uniform IFE hyperplasia without any proliferation of poorly differentiated basal cells, without increased nucleic acid staining, and without an appreciable decrease in acid DNase activity. Croton oil, as well as 0.01  $\mu$ M 12-O-tetradecanoylphorbol-13-acetate, produced an almost immediate hyperplasia of the poorly differentiated basal cells with increased intensity in staining of both nucleic acids and nearly complete deficiency in acid DNase activity. Chronic administration of 0.1 ml of a 0.5% soln of either compound 2x/wk for 7 wk produced alterations similar to those observed in the single dose experiment. The same dose of croton oil 1 wk after topical administration of 300  $\mu$ g 7,12-dimethylbenz(a)anthracene promoted tumor growth; podophyllin and acetone had no promotional effect. It is suggested that the decrease in acid DNase activity occurring almost immediately after administration of potent tumor promoters may have some importance in the mechanism of tumor promotion. (45 refs.)

**78-0195 Stimulation of the Synthesis of Mouse Epidermal Histones by Tumor-promoting Agents.** (Eng) Raineri, R. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI 53706); Simsman, R. C.; Boutwell, R. K. *Cancer Res* 37(12): 4584-4589; 1977.

In female Charles River CD-1 mice, the topical application of 17 nanomoles of the potent tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulated the incorporation of <sup>3</sup>H-lysine into epidermal histones. Max incorpo-



ration occurred 24 hr after treatment, concurrent with max DNA synthesis. The effect of TPA, phorbol, and phorbol-12,13-dibenzoate on histone synthesis were related to their tumor-promoting activities. Treatment with hydroxyurea partially prevented the phorbol ester-induced stimulation of both DNA and histone synthesis, although it had no effect on the stimulation of protein synthesis. These findings are consistent with the likelihood that phorbol ester-induced epidermal histone synthesis is the result of a coupling between DNA synthesis and histone synthesis. (22 refs.)

**78-0196 An Apparent Inactivation of Initiated Cells by the Potent Inhibitor of Two-Stage Mouse Skin Tumorigenesis, Bis(2-chloroethyl)sulfide.** (Eng) DeYoung, L. M. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI 53706); Mufson, R. A.; Boutwell, R. K. *Cancer Res* 37(12): 4590-4594; 1977.

The effects of sulfur mustard [SM, 128 nanomoles (nmol)] on biochemical changes induced by the skin tumor promoter 12-O-tetradecanoylphorbol-13-acetate (17 nmol) were examined in Charles River CD-1 mice. Epidermal-dermal p-tosyl-L-arginine methyl ester esterase activity increased similarly in mice treated with TPA alone and in mice pretreated with SM before TPA application. In both cases, the enzyme activity was four to five times the level found in acetone-treated controls. Moreover, SM pretreatment did not affect the ability of the promoter to inhibit an isoproterenol-induced accumulation of cyclic AMP. When applied 24 hr after each of three TPA applications, SM did not inhibit the three hundredfold increase in ornithine decarboxylase activity observed after a fourth application of the promoter. In tumor-induction experiments in 7,12-dimethylbenz(a)anthracene initiated (17 nmol)-animals, SM applied 24 hr after each of four TPA applications produced a 60% reduction in the number of papillomas per mouse. A similar reduction occurred when four SM applications were given during the interval between initiation and promotion. These results indicate that SM does not inhibit two-stage skin tumorigenesis by suppressing biochemical responses to TPA or through a general cytotoxic effect. Since SM has also been shown to have no effect on TPA-induced epidermal hyperplasia or inflammation, it is concluded that the compound acts primarily by inactivating initiated cells. (28 refs.)

**78-0197 Azuleno [4,5,6-cd] phenalene: A New Nonalternating Isomer of Benzo(a)pyrene.** (Ger.) Nakasuji, K. (Dept. Chemistry, Faculty Science, Osaka Univ., Toyonaka, Osaka 560, Japan); Todo, E.; Murata, I. *Angew Chem* 89(11): 821-822; 1977.

The carcinogenic and mutagenic effects of azuleno [4,5,6-cd] phenalene, whose molecular structure is similar to that of the carcinogen benzo(a)pyrene, are being studied. (9 refs.)

**78-0198 Mechanism of Action of Polycyclic Hydrocarbon Carcinogens: Immunological Aspects (Meeting Abstract).** (Eng) Stenback, F. (Eppley Inst., Omaha, NB); Curtis, G. *Scand J Immunol* 6(11): 1196; 1977. (no refs.)

**78-0199 Synthesis and Mutagenicity of Modified Chrysenes Related to the Carcinogen, 5-Methylchrysene.** (Eng) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Loy, M.; Mazzaresse, R.; Hoffmann, D. *J Med Chem* 21(1): 38-44; 1978.

The structural features required for carcinogenicity in the methylchrysene series were determined by comparing the mutagenicity of 5-methylchrysene (1) toward *Salmonella typhimurium* strain TA100 with that of other isomers. The following compounds were prepared: 1-fluoro-5-methylchrysene (2), 3-fluoro-5-methylchrysene (3), 6-fluoro-5-methylchrysene (4), 7-fluoro-5-methylchrysene (5), 9-fluoro-5-methylchrysene (6), 11-fluoro-5-methylchrysene (7), 12-fluoro-5-methylchrysene (8), 1-fluoro-4-methylchrysene (9), 6-methoxy-5-methylchrysene (10), 12-methoxy-5-methylchrysene (11), and 5-methoxychrysene (12). The methods of preparation are described in detail. A dose of 20 µg of test compound was added to a plate containing *S. typhimurium* and the S-9 fraction of livers from Arochlor-induced rats. Derivatives 2, 3, 8, 10, 11, and 12 and 5,12-dimethylchrysene were less mutagenic than 1; 4, 6, and 7 were as mutagenic; 5 was toxic; and 9 was more mutagenic than 4-methylchrysene. Structural studies indicated that the 12, 1, and 3 positions of compound 1 were involved in the metabolic activation and that the nonplanarity of 1 contributes to its mutagenicity. A sterically unhindered 12 position may be necessary for formation of a mutagenic metabolite in the adjacent 1-4 position. The ultimate mutagen derived from 1 may be a 1,2-dihydrodiol 3,4-epoxide. (29 refs.)

**78-0200 Kinetic Parameters of the Monooxygenase System in Rat Liver During the Early Stages of Chemical Carcinogenesis** (Rus) Rivkind, N. B. (Inst. Clinical and Experimental Medicine, Novosibirsk, USSR); Tsyrlow, I. B.; Gromova, O. A.; Lyakhovich, V. V. *Vopr Med Khim* 23(6): 774-777; 1977.

Benzo(a)pyrene (BP)-induced changes in the hepatic monooxygenase (MO) system of male Wistar rats were studied. Animals received BP (25 mg/kg ip, 3x/wk) for 13 wk and were then sacrificed, and NADPH-dependent reductase activity and cytochrome P-450 and P-448 contents were assessed spectrophotometrically. Prolonged exposure to the carcinogen resulted in an elevation of cytochrome P-448 content at an early stage of carcinogenesis (< 50 days) that might be due to P-448 induction. A later decrease in P-448 content was correlated with elevation of aryl hydrocarbon hydroxylase activity. (21 refs.)



- 78-0201 Metabolism of Benzo(a)pyrene by Human Lung Microsomal Fractions.** (Eng) Prough, R. A. (Dept. Biochemistry, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX 75235); Sipal, Z.; Jakobsson, S. W. *Life Sci* 21(11): 1629-1635; 1977.

To determine whether the variation in susceptibility to benzo(a)pyrene (BP) carcinogenesis between human and rat lung might be due to differences in the metabolic pattern, the metabolism of BP by lung microsomes from the two species was compared. The 15 samples of human lung were obtained at resection or autopsy. The yield of microsomal protein from human and rat lung was low compared to rodent liver. The content of NADPH-cytochrome c reductase and cytochrome P-450 was lower in human lung microsomes (HLM) than in those of the rat (RLM); the specific content of cytochrome b<sub>5</sub> was similar in both. The rate of BP monooxygenation catalyzed by HLM varied significantly among individuals and was slightly lower than that catalyzed by RLM. The rates of dihydrodiol formation obtained with the HLM and RLM were similar. However, the total dihydrodiols from incubation mixtures with HLM represented a larger percentage of the total metabolites (30%) than those obtained from RLM (19%). HLM also formed a higher percentage of the 7,8-dihydro-7,8-diol and 9,10-dihydro-9,10-diol of BP as a fraction of the total metabolites. It is hypothesized that species that have a higher rate or percentage of dihydrodiol formation might be more susceptible to polycyclic hydrocarbon-induced carcinogenesis than species with lower rates or percentages. The significant variation in the profiles of the various classes of BP metabolites formed by the HLM might reflect the clinical diagnosis and/or individual variations. (15 refs.)

- 78-0202 Cigarette Smoking, the Kerosene Stove and Lung Cancer in Hong Kong.** (Eng) Leung, J. S. (Grantham Hosp., Hong Kong). *Br J Dis Chest* 71(4): 273-276; 1977.

The high incidence of lung cancer in Hong Kong residents was examined. Of 260 consecutive lung cancer patients, 166/180 men and 45/80 women were smokers. The expected figures derived from a random survey of 2,775 adults were 106 and 9, respectively. Because cigarette smoking was associated with only half of the female patients, another potential source of inhaled carcinogen, the kerosene stove, was investigated. Forty of the women had used this type of stove daily for  $\geq 2$  yr; the expected number from a survey of 314 families was 16. It is not known whether cigarette smoking and use of a kerosene stove are synergistic in the induction of lung cancer. (2 refs.)

- 78-0203 Smoking Habits and Aryl Hydrocarbon Hydroxylase Inducibility in Patients with Malignant Tumours of the Respiratory Tract (Meeting Abstract).** (Eng) Korsgaard, R. (Dept. Lung Medicine and Res. Dept. 1, Univ. Hosp., Lund, Sweden); Stiksa, G.; Simonsson, B. G.; Trell, E. *Scand J Respir Dis [Suppl]* 99: 50-52; 1977. (8 refs.)

- 78-0204 Subcellular Events Occurring During Aryl Hydrocarbon Hydroxylase Induction: No Requirement for Metabolism of Polycyclic Hydrocarbon Inducer.** (Eng) Kano, I. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Development, NIH, Bethesda, MD 20014); Gielen, J. E.; Yagi, H.; Jerina, D. M.; Nebert, D. W. *Mol Pharmacol* 13(6): 1181-1186; 1977.

The induction of aryl hydrocarbon hydroxylase (AHH) activity in rat Reuber hepatoma H-4-II-E cells was studied with 3-methylcholanthrene and its K-region oxide and diol and with benzo(a)pyrene (BP) and 23 of its oxygenated derivatives, including 12 phenols, 3 diols, 3 quinones, 3 oxides, and 2 diol-epoxides. Compared with the parent BP molecule, the naturally occurring BP 6,12-quinone was approx as potent, the chemically synthesized 12-hydroxy derivative about one-half as potent in inducing AHH activity. The naturally occurring 7,8-oxide was also about one-half as potent as BP, and other analogs examined were even less active as inducers. Because metabolites as polar as trans-7,8-dihydroxy-7,8-dihydro-BP entered the cells as readily as BP, the poor inducing capacity of the oxygen-containing metabolites could not be attributed to decreased hydrophobicity. Their ineffectiveness compared with the parent compound indicates that the metabolism of BP is not required for AHH induction to proceed. (47 refs.)

- 78-0205 Effects of Diethyl Maleate on Aryl Hydrocarbon Hydroxylase and on 3-Methylcholanthrene-induced Skin Tumorigenesis in Rats and Mice.** (Eng) Chuang, A. H. (Dept. Biochemistry, Univ. Vermont, Coll. Medicine, Burlington, VT 05401); Mukhtar, H.; Bresnick, E. *J Natl Cancer Inst* 60(2): 321-325; 1978.

The role of aryl hydrocarbon hydroxylase (AHH) and l-glutathione (GSH) S-oxide transferase in the inactivation of polycyclic aromatic hydrocarbons in skin was investigated in two experiments. The first determined the effect of two GSH inhibitors, diethyl maleate (DEM) and L-methionine sulfoximine (MS), on the incidence and latency of 3-methylcholanthrene (3-MC)-induced skin tumorigenesis in BALB/c mice. The second determined the effect of DEM and another GSH inhibitor, cyclohexene sulfide (CHS), on AHH activity in vitro (Sprague-Dawley rat liver microsomes) and in vivo (on mouse skin). BALB/c mice were divided into six groups and given the following topical treatments in acetone: (1) 1.5 micromoles ( $\mu$ mol) 3-MC; (2) 0.3 mmol DEM; (3) DEM + 3-MC 1 hr later; (4) 5  $\mu$ mol MS; (5) MS + 3-MC 1 hr later; (6) acetone. Treatments were repeated twice weekly for 15-17 wk. By week 13, tumor incidence in Group 1 was 100%, that in Groups 3 and 5, 58% and 94%, respectively. At week 15, tumor incidence was 100% in all MS + 3-MC-treated mice also, but this did not occur in DEM + 3-MC-treated mice until week 17. A similar reduction in cumulative number of tumors was seen in Groups 3 and 5. DEM and CHS inhibited AHH activity in vitro, but CHS was much less effective than DEM. More importantly, topical application of DEM to mouse skin nearly halved AHH activity. It is



concluded that the inhibition of AHH by DEM may have been partly responsible for the increased latency time in the skin tumorigenesis experiments. (29 refs.)

**78-0206 Induction of Monooxygenases in Rhesus Monkeys by 3-Methylcholanthrene: Metabolism and Mutagenic Activation of N-2-Acetylaminofluorene and Benzo(a)pyrene.** (Eng) Thorgeirsson, S. S. (Lab. Chemical Pharmacology, Div. Cancer Treatment, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Sakai, S.; Adamson, R. H. *J Natl Cancer Inst* 60(2): 365-369; 1977.

The induction of hepatic and lung cytochrome P450-dependent monooxygenases by 3-methylcholanthrene (3-MC) was studied in male rhesus monkeys, along with the electrophoretic characteristics of the liver enzymes and the mutagenic activation of N-2-acetylaminofluorene (AAF) by liver microsomes. Hepatic N-hydroxylation of AAF increased six to sevenfold after 3-MC (80 mg/kg, ip) treatment; aryl hydrocarbon hydroxylase increased similarly in both liver and lung. The hepatic cytochrome P450 content increased by 50%, and the Soret max in the CO-hemoprotein complex shifted to 448 nanometers. Electrophoresis of hepatic microsomes from 3-MC-treated monkeys showed an increase in mol wt (54,000). Mutagenic activation of AAF by liver microsomes from untreated rhesus monkeys was low, but it increased 40-fold after 3-MC treatment. N-hydroxy-2-acetylaminofluorene did not show increased mutagenicity when tested with liver microsomes from 3-MC-treated animals. Rhesus monkeys may provide a model for evaluating the role of polycyclic hydrocarbon induction in chemical carcinogenesis and toxicity in primates. (27 refs.)

**78-0207 Prevention of 2-Acetylaminofluorene-induced Extrahepatic Short-Term Effects by 3-Methylcholanthrene.** (Eng) Danz, M. (Inst. Pathology, Friedrich-Schiller Univ., Ziegmuhlenweg 1, DDR-69, Jena, E. Germany); Urban, W.; Schmidt, A. *Exp Pathol (Jena)* 13(4/5): 262-267; 1977.

The protective effect of 3-methylcholanthrene (3-MC) on 2-acetylaminofluorene (AAF)-induced carcinogenesis in male Sprague-Dawley rat adrenals was investigated. Eleven rats received a single dose of 60 mg/kg AAF (I), 10 rats received 6 mg/kg 3-MC + 60 mg/kg AAF (II), and 12 rats served as controls (III). All substances were administered by stomach tube. A comparison of the organ wts of Groups I and II revealed a significant increase in the liver, spleen, and thymus in II. AAF stimulated the number of mitoses in the adrenal cortex 36 and 48 hr postapplication compared to controls. Furthermore, the 36-hr value in I significantly surpassed that of II and III at 48 hr. At 36 hr, there was a more-pronounced hepatic edema in Group II compared to Group I, but little change was noted by the end of the experi-

ment. These findings indicate that 3-MC modifies the early extrahepatic effects of AAF when applied simultaneously; the mechanism of action is not known. (35 refs.)

**78-0208 Phospholipid Requirement for 2-Acetamidofluorene N- and Ring-Hydroxylation by Hamster Liver Microsomal Cytochrome P-450 Enzyme System.** (Eng) Lotlikar, P. D. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Dwyer, E. N.; Baldy, W. J.; Nyce, J. *Biochem J* 168(3): 571-574; 1977.

A phospholipid requirement for 2-acetamidofluorene N and ring hydroxylation by delipidated hepatic microsomal fractions from male Syrian hamsters pretreated 24 hr previously with 3-methylcholanthrene (3-MC: 100 mg/kg ip) was investigated. When freeze-dried microsomal powder was extracted with anhydrous butan-1-ol, there was an appreciable loss of lipids without a loss of microsomal proteins. Although the fraction contained about 70% of its initial cytochrome P-448 and most of its NADPH-cytochrome c reductase activity, the extracted microsomal fraction could only N- and ring-hydroxylate 2-acetamidofluorene to 25% and 44% of control values, respectively. Addition of extracted total lipid restored both oxidations to some extent, and addition of the phosphatidylcholine fraction restored both oxidations almost completely. Dilauroyl phosphatidylcholine (0.5 mg/3 ml) was almost completely effective in restoring activity; increased concentrations, however, were inhibitory. Dipalmitoyl or distearoyl phosphatidylcholine were ineffective in restoring these oxidations. Thus, there is a requirement for phospholipid in 2-acetamidofluorene N and ring hydroxylation in the delipidated hepatic microsomal fraction from 3-MC-pretreated hamsters. (24 refs.)

**78-0209 Fluorescence Spectral Studies on the Metabolic Activation of 3-Methylcholanthrene and 7,12-Dimethylbenz(a)anthracene in Mouse Skin.** (Eng) Vigny, P. (Fondation curie-Institut du Radium, Laboratoire Curie, 11, Rue Pierre et Marie Curie, 75231 Paris, Cedex 05, France); Duquesne, M.; Coulomb, H.; Tierney, B.; Grover, P. L.; Sims, P. *FEBS Lett* 82(2): 278-282; 1977.

The metabolic activation of 3-methylcholanthrene (3-MC: 1  $\mu$ M) and 7,12-dimethylbenz(a)anthracene (DMBA: 1  $\mu$ M) on male C57Bl mouse skin was studied according to the DNA fluorescence spectra. The spectra of the DNA from 3-MC- and DMBA-treated mouse skin resembled that of the DNA isolated from 7-methylbenz(a)anthracene (7-MBA)-treated mouse skin, except for shifts in the maxima to longer wavelengths in the former. These spectra also resembled the anthracenelike spectrum obtained for DNA that had reacted with the 3,4-diol 1,2-oxide of 7-MBA. This increasing shift to longer wavelengths is consistent with the idea that there is a common mechanism of activation of these hydrocarbons



in mouse skin. These data are also consistent with the suggestion that metabolic activation gives rise to diol-epoxide in the 7,8,9,10-ring of 3-MC and in the 1,2,3,4-ring of DMBA, with the case for the latter being stronger. (17 refs.)

**78-0210 Multiplicity of Hepatic Cytochrome P-450 in Intact Microsomes: Effect of 3-Methylcholanthrene Induction.** (Eng) Mailman, R. B. (Dept. Psychiatry, Biological Sciences Res. Center, Univ. North Carolina at Chapel Hill, Chapel Hill, NC); Edmundson, W.; Muse, K.; Hodgson, E. *Gen Pharmacol* 8(4): 281-284; 1977.

The effect of 3-methylcholanthrene 25 mg/kg tid for 3 days, ip on the hepatic cytochrome P-450 of rats and mice was investigated. A small increase in total hepatic cytochrome P-450 and a significant change in the spectral characteristics of the total microsomes were noted. Subfractionation showed that two different cytochromes P-450 were present, and they were different from those of controls or phenobarbital-treated animals. Reasons for these changes are discussed. (13 refs.)

**78-0211 High-Resolution Autoradiographic Localization of 3-Methylcholanthrene-<sup>3</sup>H in the Skin of Balb/c Mice after Topical Application.** (Eng) Bibby, M. C. (Hazleton Labs. Europe Ltd., Otley Road, Harrogate, Yorkshire HG3 1PY, England); Smith, G. M. *Br J Dermatol* 97(4): 429-436; 1977.

The distribution of tritiated 3-methylcholanthrene (3-MC) in the epidermis of 3-mo-old male BALB/c mice was investigated by electron microscope autoradiography 24 hr after the application of 122  $\mu$ g <sup>3</sup>H-3-MC (1 mCi) to shaved skin on the backs of the mice. The distribution of radioactivity was nonrandom. Both the nucleus and cytoplasm of the epidermal cells were labeled, and their relative specific activities were similar. Quantification of the autoradiographs, however, indicated that there was a higher concentration of radioactivity associated with the nuclear membranes, epidermal cell membranes, and dermoepidermal junction than with either the nucleoplasm or cytoplasm. Since previous studies have demonstrated that ultrastructural changes at the dermoepidermal junction precede the macroscopic appearance of tumors, the concentration of MC or its metabolites at this junction may be related to these changes. (20 refs.)

**78-0212 Carcinogen-Protein Complexes in Mammary Gland after Administration of 3-Methylcholanthrene.** (Eng) Dickens, M. S. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Sorof, S. *Biochem Biophys Res Commun* 79(3): 713-719; 1977.

Mammary cytosolic macromolecules in BALB/c mice were examined 24 hr after ip injection of 35  $\mu$ Ci [<sup>3</sup>H]3-

methylcholanthrene (MCA) into 8-10 wk old virgin or 10-14 day pregnant mice. The cytosolic macromolecules could be resolved into at least five ranges of molecular size: > 300,000, 181,000, 88,000, 44,000, and 27,000 daltons. The only significant differences between the groups was that the virgins contained significantly more of the 27,000 dalton size class. Three species of carcinogen-protein complexes were observed: the principal complex had a modal mol wt of 83,000 and the two minor species were > 300,000 and 47,000 daltons. The minor species were more abundant in the glands from pregnant mice while the major was more abundant in the glands from virgin mice. Since in vitro incubation revealed that the 83,000 dalton complex was present in the least amount, the carcinogen is probably metabolized prior to interaction in vivo with the principal target protein. (8 refs.)

**78-0213 Establishment of Duck Cell Line Derived from Experimental Tumor Induced by 20-Methylcholanthrene.** (Eng) Kang, C. Y. (Dept. Microbiology, Univ. Texas Health Science Center, Southwestern Medical Sch., Dallas, TX 75235); Shaddock, J. A. *In Vitro* 13(12): 849-856; 1977.

The establishment of a tumor cell line from experimental tumors induced in Pekin ducks by 20-methylcholanthrene (50 mg implanted sc) is reported. Six mo postimplantation, 2/10 ducks developed tumors that grew well in both diploid growth medium and CMRL 1066; their morphology and growth characteristics were indistinguishable. An RNA-directed DNA polymerase assay of the tumor cells failed to show endogenous virus production. The cells have survived approx 80 passages, they have a doubling time of approx 19 hr and a saturation density of 30 million cells in a 100-mm dish. The chromosome pattern is very similar to that of normal duck cells. DNA hybridization between normal duck cells and the tumor line resulted in significant annealing. It is concluded that a tumor cell line of duck origin has been established. (9 refs.)

**78-0214 Patterns of Epidermal Growth and Ribosome Accumulation During 3-Methylcholanthrene-induced Epidermal Hyperplasia (Meeting Abstract).** (Eng) Mueller, S. N. (Syracuse Univ., Syracuse, NY). *Diss Abstr Int [B]* 38(5): 2001B-2002B; 1977. (no refs.)

**78-0215 Effect of Progesterone on Cell Division in Chemically Induced Endometrial Hyperplasia and Adenocarcinoma in Mice.** (Eng) Kimura, J. (Dept. Gynecology-Obstetrics, State Univ. New York, Buffalo Sch. Medicine, Buffalo General Hosp., 100 High St., Buffalo, NY 14203). *Cancer Res* 38(1): 78-82; 1978.

The effect of progesterone (P) on 3-methylcholanthrene (3-MC)-induced endometrial hyperplasia and adenocarcinoma



in ICR mice was investigated. Cotton string coated with 3-MC was implanted in the uterine cavity of the mice. A low (total: 2.5 mg) or a high (total: 35 mg) dose of P was administered at various times during a 4 to 40-wk period following 3-MC application. After serial labeling with  $^3\text{H}$  thymidine, the mice were sacrificed, and the thymidine-labeling index of endometrial hyperplasia and adenocarcinoma tissue in the P-treated and untreated (control) mice was determined autoradiographically in the 3-MC treated mice, there was a progressive increase of hyperplasia and neoplasia as a function of time. Low-dose P reduced labeling significantly in nonatypical hyperplasia and moderate atypical hyperplasia, compared with control levels. In marked atypical hyperplasia and adenocarcinoma, irrespective of the histological grade, labeling was not reduced. With high-dose P, marked morphological alterations with degenerative changes were observed in atypical hyperplasia and in differentiated adenocarcinoma. Cancer cells, however, were still maximally labeled. It is concluded that the effect of P on nonatypical hyperplasia and moderate atypical hyperplasia is mitotic arrest, but that the effect on marked atypical hyperplasia and adenocarcinoma is morphological and cytological alterations. (22 refs.)

**78-0216 The Induction of Sister Chromatid Exchanges by Cyclophosphamide in the Presence of Differently Induced Microsomal Fractions of Rat Liver.** (Eng) de Raat, W. K. (Central Lab. TNO, P. O. Box 217, Delft, Netherlands). *Chem Biol Interact* 19(1): 125-131; 1977.

The induction of sister chromatid exchanges (SCE) in rat liver by cyclophosphamide (CP) was investigated 5 days after administration of three co-inducers: 500 mg/kg ip Aroclor 1254, 80 mg/kg ip 3-methylcholanthrene (3-MC), and 0.1% phenobarbital in the drinking water. The effect of four S-9 fractions (supernatants of the rat liver homogenates, each containing 1 of the 3 co-inducer compounds and 1 uninduced) and coenzyme solution, with or without CP, on the survival of Chinese hamster ovary (CHO) cells was determined. In the presence of 0.02 or 0.04 ml S-9 fraction/ml medium and of 0.05 ml coenzyme/ml medium, the number of surviving cells was similar to that of controls. CP was converted into SCE-inducing metabolites, and the induction of SCE was strongly dependent on the induction of microsomal enzymes. Without S-9, no extra SCE induction was noted. The difference in SCE induction corresponded to differences in CP metabolism, which was measured as the decrease in NADPH induced by CP. 3-MC resulted in a decrease in NADPH of only 33 nanomole (nmol)/mg S-9 protein/hr. The corresponding figures for phenobarbital and Aroclor 1254 were 160 and 197 nmol, respectively. The benzo(a)pyrene hydroxylase activity for the uninduced S-9 fraction was 6.1 to 7.3 nmol/mg S-9 protein/hr. The respective figures for 3-MC, phenobarbital, and Aroclor 1254 were 12.8-13.4, 5.0-5.8, and 10.3-12.5, respectively. Thus, the metabolism of CP is induced by phenobarbital type inducers, indicating that cytochrome P-450 must be involved. (19 refs.)

**78-0217 Enhancement of Artificial Lung Metastases by Cyclophosphamide: Pharmacological and Mechanistic Considerations.** (Eng) Peters, L. J. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Mason, K. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 397-410; 1977.

The pharmacodynamics of the effects of cyclophosphamide (CP) on artificial lung metastases were studied, and the actions of the drug and irradiation were compared. Pretreatment of C3Hf/Bu mice with CP (150  $\mu\text{g/g}$  sc or iv) increased the lung colony-forming efficiency (CFE) of iv-injected tumor cells (a methylcholanthrene-induced fibrosarcoma) in a dose-dependent fashion. The effect was slightly greater when CP was given sc. By both routes, the effect was constant from 1 to 7 days prior to tumor cell injection. Two equally divided doses of CP were less effective than a single dose, but some cumulative effect was present with a dose interval of 48-96 hr. Increasing the biotransformation rate of CP decreased its effect on CFE, whereas inhibition of metabolism further increased CFE. Premetabolism of CP in vitro did not abolish its action. These results suggest that the integrated total exposure to CP metabolites determines the drug's effectiveness. The increase in CFE caused by a moderate 150- $\mu\text{g/g}$  dose of CP was additive to that of a 1,000-rad dose of whole-body radiation. Retention of tumor cells in the lungs 24 hr after injection was much greater in CP-treated mice than in irradiated mice, but the ultimate number of lung colonies formed was less. It is concluded that the major effect of CP is to condition the lungs in such a way as to promote lodgement and survival of cells soon after iv dissemination. An idiosyncratic reaction to one of its metabolites may explain the marked effect of CP on CFE compared with other alkylating agents. (21 refs.)

**78-0218 Acute Leukemia after Busulphan.** (Eng) Stott, H. (Medical Res. Council Tuberculosis and Chest Diseases Unit, Brompton Hosp., Fulham Road, London SW3 6HP, England); Fox, W.; Girling, D. J.; Stephens, R. J.; Galton, D. A. *Br Med J* 2(6101): 1513-1517; 1977.

The results of a follow-up of 726 bronchial carcinoma patients who were treated postoperatively, eight times per day, with 0.5 mg busulfan (BUS), 25 mg cyclophosphamide (CP), or placebo are presented. After the first 10 days, the dosage was reduced to six tablets daily; this dosage was then halved at 11 mo because of toxicity. Although no cases of leukemia were noted during the first 5 yr, by 9 yr three cases of myelomonocytic leukemia (62, 63, and 64 mo) and one case erythroleukemia (97 mo) had occurred all in patients taking BUS. This amounted to an incidence of 5.8% in the 69 BUS-treated patients who survived 5 yr. The 4 patients were among the 19 BUS-treated patients who developed pancytopenia during chemotherapy: 8 had survived to 5 yr, and the



leukemia patients were among these 8. The leukemia patients had received a mean dose of 486 mg BUS over 453 days for an av daily dose of 1.1 mg, compared to an av daily dose of 2.2 mg (546 mg in 250 days) in the four other pancytopenic patients surviving at 5 yr. None of the leukemia patients had received other cytotoxic chemotherapy or radiation treatment. Nineteen other patients (6 BUS, 5 CP, 8 placebo) developed at least one other primary malignant neoplasm in addition to the original bronchial carcinoma (8 gastrointestinal tract tumors, 5 genitourinary tract tumors, 1 tumor in the opposite lung with different histology, 2 epitheliomas, 1 tumor of the cecum and pelvic colon, 1 of the bladder and opposite lung with different histology, and 1 of the colon and prostate). It is suggested that BUS is leukemogenic, but its mode of action is not known. (30 refs.)

**78-0219 Mutagenic Activity of Major Mammalian Metabolites of Cyclophosphamide Toward Several Genes of *Escherichia coli*.** (Eng) Ellenberger, J. (Zentral-laboratorium für Mutagenitätsprüfung, Breisacher Strasse 33, 7800 Freiburg im Breisgau, W. Germany); Mohn, G. R. *J Toxicol Environ Health* 3(4): 637-650; 1977.

Representative intermediates in the metabolism of cyclophosphamide (CP), a drug that is not mutagenic unless metabolically activated, were assayed for their direct mutagenicity toward *Escherichia coli* 343/113. The compounds tested were 4-hydroperoxycyclophosphamide and the two urinary metabolites carboxyphosphamide and 4-ketocyclophosphamide. The degradation products of 4-hydroxycyclophosphamide, phosphoramidate mustard, acrolein, and normitrogen mustard were also tested. Stationary cell suspensions were treated for 180 min at 37 C with different concentrations of each test compound. The induction of forward mutations from 5-methyltryptophan sensitivity to resistance (MTR) and from *galR*<sub>18</sub> to *gal*<sup>±</sup>, as well as back mutations from *arg*<sub>36</sub> to *arg*<sup>±</sup>, was measured by plating aliquots of the treated bacterial population on different selective mutation media. Except for acrolein, all the CP metabolites were directly mutagenic toward *E. coli* 343/113. With all substances, *arg*<sup>±</sup> mutations were most frequent, followed by *gal*<sup>±</sup> and MTR mutations. This indicates that base-pair substitution type mutations are predominant. However, the mutagenic potential of the compounds varied greatly at concentrations between 0.1 and 20 mM. The results show that CP is degraded to compounds that are directly mutagenic and that this mutagenicity is retained and even enhanced through further metabolic steps to produce the compound with the highest mutagenicity, normitrogen mustard. (28 refs.)

**78-0220 Cancer and Teratogenesis: Infrequent Occurrence after Medical Use of Immunosuppressive Drugs.** (Eng) Symington, G. R. (Clinical Res. Unit, Walter and Eliza Hall Inst. Medical Res., Post Office, Royal Melbourne Hosp., Victoria 3050, Australia); Mackay, I. R.; Lambert, R. P. *Aust NZ J Med* 7(4): 368-372; 1977.

The occurrence of cancer and fetal abnormalities was examined following medical treatment 133 patients (941 women between 1963 and 1975) with azathioprine and/or 6-mercaptopurine (114), azathioprine and cyclophosphamide in sequential courses (11), and cyclophosphamide (8). Two patients developed squamous cell carcinoma of the skin; one had received azathioprine and one cyclophosphamide, each in combination with prednisolone. Two benign neoplasms and six keratoses were also recorded. All eight patients had been treated with azathioprine and prednisolone. After close of the study, one of the patients with carcinoma of the skin developed a carcinoma of the colon; two additional patients (one of whom had had a keratosis) also developed skin cancer. Nine women received azathioprine during pregnancy; no teratogenic effects were observed. One woman received cyclophosphamide for 5 wk; the infant was normal except for a small hemangioma of the thigh and an umbilical hernia. A normal child was fathered by a patient who received azathioprine for 7 wk prior to conception. Seventy patients were examined and found to have a marked suppression of cell-mediated immunity. It is concluded that these drugs did not carry any substantial risk of cancer or teratogenesis during the 4 yr observation period. (37 refs.)

**78-0221 Cytogenetic Effects of Myleran In Vivo on Bone-Marrow Cells from Male Mice.** (Eng) Leonard, A. (Dept. Radiobiology, Mammalian Genetics Lab., C.E.N.-S.C.K., B-2400 Mol, Belgium); Leonard, E. D. *Mutat Res* 56(3): 329-333; 1978.

The cytogenetic effects of Myleran (busulfan; 1,4-di(methanesulfonoxybutane)) were examined in bone marrow cells from male BALB/c mice inoculated ip with 5, 10, 20, or 40 mg/kg of the compound. Bone marrow samples were prepared 24 hr later. Most (71%) of the structural aberrations in the affected cells were of the chromatid type. The number of cells exhibiting aberrations as well as the total number of abnormalities increased with the dose. The number of abnormal cells was 12/200, 21/200, 53/200, 79/200, and 0/200 at 5, 10, 20, 40, and 0 mg/kg, respectively, and the corresponding total number of anomalies was 14, 29, 68, 141, and 0. The cytogenetic effect of Myleran was studied in bone marrow samples prepared 1, 2, 4, or 10 days after a single ip injection of 40 mg/kg. The frequency of chromatid and chromosomal aberrations was max 2 days after the injection, and it decreased sharply at longer intervals. The chromatid and isochromatid gaps represented 63% of the total number of abnormalities. (18 refs)

**78-0222 Azathioprine and Breast Carcinoma (Letter to Editor).** (Eng) Krutchik, A. N. (Univ. Texas System Cancer Center, Houston, TX 77030); Buzdar, A. U.; Tashima, C. K. *JAMA* 239(2): 107-108; 1978.



The case reports of two women, aged 46 and 38 yr, who developed breast cancer following azathioprine treatment are reported. The former had been treated with azathioprine for chronic active hepatitis 6 yr before the carcinoma diagnosis. The latter had been treated in conjunction with a donor-related renal transplant 4 yr previously; she had Paget's disease of the nipple and intraductal adenocarcinoma. (4 refs.)

**78-0223 Metastasis and Chemotherapy, with Reference to Permeability of the Microcirculation System.**

(Eng) Sato, H. (Dept. Oncology, Res. Inst. Tuberculosis, Leprosy and Cancer, Tohoku Univ., Sendai, Japan); Suzuki, M. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P. Stansly, P.; Garattini, S.; Lewis, M. C.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol., 5, 517 pp.; 145-149; 1977.

Model experiments on the production of brain metastases in rats by transplantation of tumor cells from several strains of rat ascites hepatomas into the carotid artery are described. Each strain has different ascitic features, and each is correlated with the four types of brain metastases that resulted. In other experiments, a model of meningeal leukemia formed by the direct injection of  $10^6$  DBLA-6 ascites leukemia cells onto rat brain was used to determine the effect of the blood-brain or blood-cerebrospinal fluid (B-CSF) barrier on chemotherapy. Cells were transplanted on day 0, daunomycin (DM) was administered iv three times a day by 1/2 regimens on days 1-4 (1-mg doses on days 1-3, or 2-mg doses on days 2-4), and the animals were sacrificed on day 6. The growth of leukemia cells was inhibited markedly in the dura mater, but not in the subarachnoid space. Fluorescein cineangiography showed that there was a B-CSF barrier in the subarachnoid space. When the blood pressure of the rats (90 mm Hg) was increased 100% by angiotensin ( $60 \mu\text{g/kg}$  iv for 3 min) prior to DM treatment, the growth of the leukemia cells was inhibited markedly not only in the dura mater, but also in the subarachnoid space and brain. Thus, there is a correlation between the B-CSF barrier and delivery of drugs to tumor cells growing outside blood vessels. (9 refs.)

**78-0224 The Incidence of Cervical Cancer and Duration of Oral Contraceptive Use.** (Eng) Peritz, E. Kaiser-Permanente Contraceptive Drug Study, Medical Center, 1515 Newell Ave., Walnut Creek, CA 94596; Ramcharan, S.; Frank, J.; Brown, W. L.; Huang, S.; Ray, R. *Am J Epidemiol* 106(6): 462-469; 1977.

The association of carcinoma of the cervix and oral contraceptive use was examined in 14,567 women. A positive association was established after controlling the values for the effects of age, education, marital status, number of Pap smears before entry, religion, smoking, and selected infections. The association persists when cases of dysplasia are added to the cancer cases. These results suggest that the null

hypothesis should be rejected. The importance of these data must await the results of a further study in which the sexual behavior of users and nonusers will be taken into account. (29 refs.)

**78-0225 Malignant Melanoma and Oral Contraceptive Use among Women in California.** (Eng) Beral, V. (Dept. Medical Statistics and Epidemiology, London Sch. Hygiene and Tropical Medicine, Keppel St., London, WC1, England); Ramcharan, S.; Faris, R. *Br J Cancer* 36(6): 804-809; 1977.

Two groups of California women were studied to determine the association between oral contraceptives (OC) and malignant melanoma. The first group of 17,942 women was recruited from a health plan membership. In the age range 25-34, melanomas were only diagnosed in women who were ever-users of OC, especially for  $> 4$  yr. In the age range 35-44, the incidence of malignant melanoma was higher in the never-users than in those who had used OC for  $> 4$  yr. At ages 45-54 yr, OC users had a higher incidence; in this range, ever-users of estrogens other than OC also had a higher incidence of the disease than never-users. There was an increased risk of malignant melanoma among women with light-colored eyes compared to those with brown eyes, but, regardless of eye color, melanoma incidence was increased in the OC users. The second group comprised 37 women who developed malignant melanomas between January 1968 and June 1976. There was an excess of OC use in this group: the risk for ever-users vs never-users was 1.8:1. When these two groups were combined, ever-users had the disease had an excess of lesions on the lower limbs. There was no definite association between brand of OC or its estrogen or progestogen content and the occurrence of malignant melanoma. (17 refs.)

**78-0226 Large Migrating Hepatic Adenoma Associated with Use of Oral Contraceptives.** (Eng) Weissman, I. (Univ. Illinois McKinley Hosp., Champaign, IL); Russo, M. J.; Brunner, R. W. *Ill Med J* 152(6): 483-486; 1977.

The case report of a 26-yr-old woman with a large migrating benign hepatic adenoma is presented. She had a history of taking birth control pills for 6 yr. The differential diagnosis of any abdominal mass in a young woman using oral contraceptives should include benign liver tumors. (9 refs.)

**78-0227 Bilateral Breast Cancer Associated with Clomiphene (Letter to Editor).** (Eng) Bolton, P. M. (Royal Brisbane Hosp., Brisbane, 4029 Queensland, Australia). *Lancet* 2(8049): 1176; 1977.

Case reports are presented for two women who developed synchronous bilateral breast cancer after taking clomiphene (50 mg/day during the menstrual cycle) because of infertility. Neither patient had a family history of breast cancer. (9 refs.)



**78-0228 Breast Cancer and the Use of Rauwolfia Derivatives in a Population of Hypertensive and Normotensive Women (Meeting Abstract).** (Eng) Farber, M. D. (Univ. California, Los Angeles, CA). *Diss Abstr Int [B]* 38(5): 2131B; 1977. (no refs.)

**78-0229 Fine Structural, G-6-PD Isoenzyme, and HaLV gs Antigen Studies of Poly I/C and Antiestrogen Treated DES-induced Hamster Renal Tumors.** (Eng) Dodge, A. H. (Dept. Anatomy, Stanford Sch. Medicine, Stanford Univ., Stanford, CA 94305). *Eur J Cancer* 13(12): 1377-1387; 1977.

The effect of sc and ip injection of poly I/C (polyriboinosinic/polyribocytidylic acid), po administration of the antiestrogen ICI 46, 474 [the trans-isomer of 1-(p- $\beta$ -dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene], and sc administration of the antiestrogen U-11,100A (nafoxidine hydrochloride) on diethylstilbestrol (DES)-dependent and DES-independent renal tumors in Syrian hamsters was investigated. The tumors were induced by subpannicular implantation of 30 mg DES for  $\geq$  250 days. Treatment of animals every other day with 1 mg/ml poly I/C sc near the autonomous tumors and 1 mg/ml ip resulted in a return of the glucose-6-phosphate dehydrogenase (G-6-PD) isoenzymes pattern to that of the surrounding tissue and to that of the kidneys of normal non-DES-treated hosts. Tumors between 1 and 5 mm regressed after poly I/C treatment. Treatment of animals with ICI 46,474 (0.1 ml/day of a 0.6-mg/ml mixture for 8-60 days) U-11,100A (1 ml/day of a 100-mg/ml solution for 5 days) also resulted in a return of the G-6-PD pattern to that observed in the adjacent kidney. Poly I/C reduced the expression of Harvey leukemia virus group-specific antigen. The cytologic changes in the DES-dependent tumors resulted from treatment by poly I/C and the antiestrogens. DES-independent tumors treated with poly I/C and areas of unchanged tumor tissue and regions with a great deal of necrosis; however, their growth was not inhibited. The G-6-PD pattern could be useful as a marker isoenzyme to characterize a stage of tumorigenesis that is vulnerable to inhibitor treatment. (16 refs.)

**78-0230 Transplacental Effects of Diethylstilbestrol on the Human Male Fetus: Abnormal Semen and Anatomical Lesions of the Male Genital Tract.** (Eng) Gill, W. B. (Dept. Surgery, Univ. Chicago, Chicago, IL); Schumacher, G. F.; Bibbo, M. *In Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, DC.* Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; pp. 39-46; 1977.

The effects of diethylstilbestrol (DES) on the male genital tract were examined in a follow-up study of the male offspring of women treated with DES or placebos during pregnancy. DES was administered po at 5 mg/day starting with the 7th week of gestation and increased by 5 mg/day every

other week to a max dose of 150 mg/day by the 34th week. Epididymal cysts, hypotrophic testes, capsular induration of the testes, and microphallus were present in  $> 25\%$  of 163 DES-exposed men compared with 6.5% of 168 controls. Spermatozoa analysis revealed severely pathological changes in 28% of 39 DES-exposed men and 0% of 25 controls. Pathological spermatozoa were found in 46% of 39 DES-exposed men and in 12% of 25 controls. In 28% of the exposed subjects, pathological semen was associated with genital abnormalities on physical examination. Urine specimens, prostatic fluids, and aspirates from epididymal cysts were negative for tumor cells. (12 refs.)

**78-0231 Transplacental Carcinogenesis: Prenatal Diethylstilbestrol (DES) Exposure, Clear Cell Carcinoma and Related Anomalies of the Genital Tract in Young Females.** (Eng) Welch, W. R. (Dept. Pathology, Harvard Medical Sch., Boston, MA); Barnes, A. B.; Robboy, S. J.; Herbst, A. L. *In: Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, DC.* Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; pp. 47-50; 1977.

The epidemiology, diagnosis, and therapy of vaginal or cervical clear cell adenocarcinomas associated with in utero diethylstilbestrol (DES) exposure are discussed on the basis of the 150 cases accessioned by a Chicago tumor registry. In every case for which accurate maternal histories were available, the drug was administered prior to the 18th week of gestation. A marked increase in cancer frequency after age 14 suggests that an event related to puberty, such as ovarian estrogen secretion, may play a role in tumor development. Microscopically, the tumors resemble the clear cell ovarian and endometrial cancers of older women. Of the nonmalignant anomalies induced by DES, vaginal and cervical ridges occur in approx 20% and vaginal adenosis in 35%-90% of the exposed population. The latter is more prevalent in the offspring of women who took DES prior to the 18th week of gestation. The possibility that adenosis is associated with squamous cell malignancy is discussed briefly. (6 refs.)

**78-0232 Invasive Squamous Cell Carcinoma of the Cervix in a Diethylstilbestrol-exposed Offspring (Letter to Editor).** (Eng) Lamb, E. J. (Dept. Gynecology and Obstetrics, Stanford Univ. Medical Center, Stanford, CA 94305). *Am J Obstet Gynecol* 129(8): 924-925; 1977.

The case report of a 21-yr-old woman with invasive squamous cell carcinoma of the cervix is presented. Her mother had taken 25 mg diethylstilbestrol (DES) daily beginning at 6 wk of gestation and ending possibly as late as 20 wk. This is the second reported association between DES exposure and squamous cell carcinoma of the cervix. (7 refs.)



**78-0233 The Effect of Various Doses of Oral Oestradiol-valerate and Oestriolsuccinate on Urine Calcium/Creatinine, Serum FSH and Endometrium in Castrated Women.** (Eng) Rauramo, L. (Dept. Obstetrics and Gynecology, Univ. Hosp., Turku, Finland); Punnonen, R.; Lauslahti, K.; Gronroos, M. *Acta Obstet Gynecol Scand* 56(4): 363-366; 1977.

The effect of various doses of estradiol valerate (EV) and estradiol succinate (ES) on urinary calcium/creatinine, serum follicle-stimulating hormone (FSH), and the endometrium was investigated in two women, aged 31 and 35 yr, who had undergone bilateral oophorectomy 12 yr previously. Six weeks of ES (2 mg/day) had minimal effect on the endometrium. Treatment with EV (1 mg/day) or with EV + ES caused weak endometrial proliferation. With 2 mg/day EV, proliferation was observed in the surface epithelium, glands, and stroma. When this treatment was continued for three 6-wk periods separated by 2-wk intervals, endometrial proliferation at the end of the third treatment was the same as that at the end of the previous two. Marked proliferation was observed when EV + ES (each, 2 mg/day) were given for 6 wk. Six weeks of estrogen treatment decreased urine CA except when 2 mg/day EV was used. The urine Ca/creatinine ratio decreased after 6 wk of treatment except with 1 mg EV + 2 mg ES daily and 2 mg/day EV. After 6 wk of estrogen treatment, plasma FSH levels were always less than or equal to the levels obtained without estrogen treatment. (9 refs.)

**78-0234 The Effect of Subcutaneous Administration of Oestrogens on Plasma Oestrogen Levels and Tumour Incidence in Female Rats.** (Eng) Blankenstein, M. A. (Dept. Biochemistry II, Medical Faculty, Erasmus Univ. Rotterdam, P.O. Box 1738, Rotterdam, Netherlands); Broerse, J. J.; de Vries, J. B.; van den Berg, K. J.; Knaan, S.; van der Molen, H. J. *Eur J Cancer* 13(12): 1437-1443; 1977.

The hormonal status of female Wistar WAG/Rij rats, either intact or after hysterectomy, was studied during treatment with various estrogens. Estrogens were implanted sc in the dorsal region of the neck in pellet form. When 5 mg of 17 $\beta$ -estradiol-3-benzoate was pressed into a pellet with 15 mg cholesterol and implanted (1-4 pellets/animal), blood samples taken at 3 days showed a dose-dependent high level of 17 $\beta$ -estradiol that decreased over the next 27 days. Results were essentially the same for ovariectomized and intact animals. Within a latent period of 10-12 mo, 34/37 animals developed pituitary tumors, and 7 animals developed mammary tumors. In another experiment, pellets of 2.5 or 1.0 mg 17 $\beta$ -estradiol were either prepared as described previously, mixed with cholesterol and oil and placed into tubing cut in 2- to 3-mm segments, or mixed with cholesterol and paraffin and prepared as tubules. Implantation of the pressed pellets gave higher plasma levels over 160 days than implantation of the two types of tubules. In a third experiment, estrogen release from tubules prepared with paraffin and 17 $\beta$ -estradiol or 17 $\alpha$ -ethynylestradiol were compared in ovariectomized

and intact animals. There was no difference in the rate of estrogen released by either compound in intact and ovariectomized rats. (22 refs.)

**78-0235 Long-Term Effects of Prenatal and Neonatal Administration of 5 $\beta$ -Dihydrotestosterone on Normal and Neoplastic Mammary Development in Mice.** (Eng) Yanai, R. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Mori, T.; Nagasawa, H. *Cancer Res* 37(12): 4566-4459; 1977.

The long-term effects of 5 $\beta$ -dihydrotestosterone (5 $\beta$ -DHT) on mammary glands were studied in female SHN mice infected with mammary tumor virus. 5 $\beta$ -DHT was administered sc to mothers for 4 days from days 12 to 15 of pregnancy (prenatal treatment) and to pups for 5 days of postnatal life (neonatal treatment) at daily doses of 1 mg and 200  $\mu$ g, respectively. Neonatal treatment resulted in marked stimulation of spontaneous mammary tumorigenesis: all neonatally treated mice had palpable mammary tumors by age 6.2 mo, when mammary tumor incidence in control mice and in mice treated prenatally with 5 $\beta$ -DHT was 21.1% and 6.3%, respectively. Furthermore, neonatal treatment promoted normal and preneoplastic mammary growth and pituitary prolactin secretion and induced the ovarian anovulatory syndrome in all mice. Prenatal treatment also increased the number of mammary hyperplastic alveolar nodules and induced a delayed anovulatory syndrome. These results demonstrate that perinatal treatment with 5 $\beta$ -DHT, which is thought to be biologically inactive in adult mice, can induce irreversible changes in the mammary glands, pituitary gland, ovaries, and genital tracts. (10 refs.)

**78-0236 The Role of the Anterior Pituitary Gland in Progesterone-induced Proliferative Mammary Gland Changes in the Beagle.** (Eng) Graf, K. J. (Free Univ. Berlin, Klinikum Charlottenburg, Dept. Internal Medicine, Spadauer Damm 130, 1000 Berlin 19, W. Germany); El Etreby, M. F. *Arzneim Forsch* 28(1): 54-58; 1978.

The effect of several synthetic progestagens on prolactin (PRL) and growth hormone (GH) secretion in female beagle dogs was investigated. Three dogs that had been oophorectomized-hysterectomized 4-5 mo previously were treated with cyproterone acetate (CPA) (100 mg/kg/day po) for 4 wk. There was no significant difference between pre- and post-treatment PRL levels or between levels in treated and untreated animals. Similar findings were obtained with GH. Immunoenzyme-cytochemical investigations revealed no differences in PRL-producing cells in treated and untreated dogs. However, GH cells from treated animals were increased, relative to other cell types, in the anterior pituitary. The mammary glands of CPA-treated animals showed ductal proliferation as well as hyperplasia and desquamation of the epithelial tissue. There was also marked lobuloalveolar devel-



opment and activation of the stroma. In another experiment, blood samples were taken from intact females 2 wk after the third im injection of 6, 60, or 150 mg/kg norethisterone enanthate. Although PRL concentrations varied with dose, all were within the range of controls. PRL levels in controls did not vary with degree of mammary gland enlargement. However, in untreated controls, GH levels were higher in animals without clinical signs of mammary gland enlargement whereas in treated animals, these levels were higher in those with signs of enlargement. (25 refs.)

- 78-0237 Multiple Oncogenesis of Neural Crest Cells by Steroids in Suckling Mice.** (Eng) Nozue, T. (Dept. Anatomy, Tokyo Medical and Dental Univ., Tokyo, Japan); Kayano, T. *Experientia* 33(12): 1640-1641; 1977.

The effects of hydrocortisone (cortone acetate) and androgen (androgendepot; enanthic acid testosterone, 50 mg/ml; capric acid testosterone, 50 mg/ml) on suckling ICR-JCL mice were determined. Within 24 hr of birth, 50 mice were inoculated ip with 35 mg/kg hydrocortisone, 10 mice with a lower dose. Similarly, 40 mice were inoculated ip with 670 mg/kg androgen, 10 mice with a lower dose. Mice treated with the higher doses developed morphological and histological abnormalities similar to those observed with mitomycin C. Both steroids produced similar effects. Tumors were observed in the periosteum, perichondrium, bone marrow, walls of the blood vessels, heart, spleen, parotid glands, submandibular glands, teeth, oral mucosa, stomach, intestine, liver, lungs, pancreas, adrenals, thyroid, thymus, vibrissae, skin, eyes, craniospinal nerves and ganglia, sympathetic nerves and ganglia, nerve plexus of the periosteum, pleura, pia mater, brain, kidneys, uterus, and testis. All these tissues are colonized by cells of neural crest origin. These abnormalities were generally absent in the lower-dose animals. The phase of the cell cycle may influence cell-surface properties and phenotypic expression in systems mediated by cyclic AMP. Steroids may induce errors in transcription, resulting in mutation. A similar process probably occurs with mitomycin C. (20 refs.)

- 78-0238 Reports on Bioassays of Aldrin and Dieldrin for Possible Carcinogenicity.** (Eng) Fredrickson, D. S. (NIH, Bethesda, MD 20014). *Fed Regist* 43(11): 2450-2451; 1978.

The carcinogenicity of aldrin and dieldrin was assayed in Osborne-Mendel rats and B6C3F1 mice. Groups of 50 rats of each sex were given 30 or 60 ppm aldrin for 74-80 wk followed by 32-38 wk of observation. Groups of 50 mice of each sex received 3, 4, or 6 ppm aldrin for 80 wk and were followed for 10-13 wk. Follicular cell adenomas and thyroid carcinoma were noted in male and female rats, and adrenal cortical adenomas were noted in female rats. However, the only significant tumor incidence occurred in male mice who had a dose-related increase in hepatocellular carcinomas. Groups of 50 rats of each sex received 29 or 65 ppm dieldrin for 80

wk, and they were observed for an additional 30-31 wk. Equal numbers of mice received 2.5 or 5 ppm dieldrin for 80 wk, and they were observed for 10-13 wk. There was an increase in adrenal cortical adenomas or carcinomas in female rats but this could not be definitely related to treatment. Male mice had a significant dose-related incidence of hepatocellular carcinomas. Groups of 24 Fischer 344 rats of each sex also received either 2, 10, or 50 ppm dieldrin for 104-105 wk. Although a variety of neoplasms were noted, none were related to treatment. (no refs.)

- 78-0239 Report on Bioassay of Photodieldrin for Possible Carcinogenicity.** (Eng) Fredrickson, D. S. (NIH, Bethesda, MD 20014). *Fed Regist* 42(232): 61316-61317; 1977.

The carcinogenicity of photodieldrin was assayed in male and female Osborne-Mendel rats and B6C3F1 mice. Male rats received 5 or 10 ppm photodieldrin in the diet for 80 wk; females received these concentrations for 30 wk and 3.4 or 7.5 ppm thereafter; mice received 0.32 or 0.64 ppm in the diet for 80 wk. Although benign mammary tumors, malignant thyroid tumors, and hemangiomas occurred in the rats, the incidence was not always significant; no significant tumors were noted in the mice. It is concluded that under these conditions, photodieldrin is not carcinogenic in these species. (no refs.)

- 78-0240 Study of Lymphocyte Karyotypes in Patients with Benzene-induced Myelopathy Twelve Years after Exposure.** (Ita) Pollini, G. (Istituto di Medicina del Lavoro dell'Universita de Pavia, Pavia, Italy); Biscaldi, G. *P. Med Lav* 68(4): 308-312; 1977.

The peripheral blood lymphocytes of four patients with benzene-induced myelopathy were examined karyotypically 12 yr after diagnosis, and the findings were compared with those of previous studies of these patients. No statistically significant alterations were found at this last examination. (10 refs.)

- 78-0241 Non-industrial Exposure to Benzene as Leukemogenic Risk Factor.** (Eng) Brandt, L. (Dept. Internal Medicine, Univ. Hosp., S-221 85 Lund, Sweden); Nilsson, P. G.; Mitelman, F. *Lancet* 2(8047): 1074; 1977.

The case reports of a 16-yr-old boy with acute monocytic leukemia, a 59-yr-old woman with acute undifferentiated leukemia, and a 36-yr-old man with acute myeloid leukemia are summarized. These patients had been exposed to benzene in a lacquer, as a cleanser, and in a mixture with gasoline, respectively. It is suggested that the exposure could have been responsible for the leukemia. (5 refs.)



78-0242 **Changes in Polyamine Levels and Protein Synthesis Rate during Rat Liver Carcinogenesis Induced by 4-Dimethylaminoazobenzene.** (Eng) Perin, A. (Inst. General Pathology, Univ. Milan, Via Mangiagalli, 31, 20133); Sessa, A. *Cancer Res* 38(1): 1-5; 1978.

Hepatic putrescine, spermidine, and spermine concentrations were determined in male Sprague-Dawley rats fed a commercial diet, a Miller diet, or a Miller diet containing 0.06% 4-dimethylaminoazobenzene (DAB). In control rats, putrescine and spermidine levels decreased with increasing age; spermine levels decreased only slightly. The same changes were observed in rats fed only the Miller diet. In rats fed DAB, putrescine levels increased after 15 days to a max at 90 days, when 2- to 4-mm tumors were apparent. Spermidine levels increased after 60 days and remained high for 90 days; further increases were noted in the 5- to 8-mm and 10- to 20-mm tumors that developed after 120 and 150 days, respectively. Spermine levels also increased significantly in these tumors. In the 25-mm tumors noted after 180 days, the polyamine concentrations decreased, probably as a result of necrosis. The rate of liver protein synthesis in DAB-treated animals increased after 60 days on the diet but it decreased in the large tumors apparent after 180 days. Protein synthesis correlated with polyamine concentrations in both control and tumor-bearing rat liver; synthesis also correlated with spermidine and spermine concentrations. Values for putrescine, spermidine and spermine in the urine of tumor-bearing rats were 1.6, 4.2 and 4.2 times those of control rats, respectively. Similar increases were observed when the values were expressed as  $\mu\text{g}/\text{mg}$  creatine. (38 refs.)

78-0243 **The Large Bowel Carcinogenic Effects of Hydrazines and Related Compounds Occurring in Nature and in the Environment.** (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105). *Cancer (Suppl)* 40(5): 427-2431; 1977.

Five substituted hydrazines that induce large bowel and other types of cancer in laboratory animals are described. Two of these compounds are 1,1-dimethylhydrazine, a tobacco ingredient, and methylhydrazine, formed from a chemical present in the edible wild mushroom *Gyromitra esculenta*. A large segment of the human population is, therefore, exposed to them. The other three chemicals, 1,2-dimethylhydrazine dihydrochloride, 1-methyl-2-butylhydrazine dihydrochloride and trimethylhydrazine hydrochloride, are manufactured synthetically only and apparently are not found in substantial quantities in the environment. (42 refs.)

78-0244 **Morphogenesis of Early 1,2-Dimethylhydrazine-induced Lesions and Latent Period Reduction of Colon Carcinogenesis in Mice by a Variant of *Citrobacter freundii*.** (Eng) Barthold, S. W. (Section

Comparative Medicine, Yale Univ. Sch. Medicine, New Haven, CT 06510); Jonas, A. M. *Cancer Res* 37(12): 4352-4360; 1977.

The morphogenesis of 1,2-dimethylhydrazine (DMH)-induced colonic lesions in outbred NIH Swiss mice was determined for up to 5 mo of treatment (20 mg/wk, sc). In addition, the effect of hyperplasia on DMH carcinogenesis was evaluated by introducing a transient hyperplastic stimulus to the colon during the chronic weekly treatment regimen. The hyperplastic stimulus was transmissible murine colonic hyperplasia, which is caused by a variant of *Citrobacter freundii*. In control mice not receiving the bacterium, weekly injections of the carcinogen for 2 mo induced neoplastic changes in all segments of the colon and in both sexes. The changes increased in frequency and severity with time. Diffuse mucosal hyperplasia and chronic inflammatory and degenerative changes were also associated with DMH after prolonged treatment. The hyperplastic stimulus of *C. freundii* reduced the latent period for the appearance of early DMH tumors, but it had no influence on established DMH tumors. (38 refs.)

78-0245 **Cytotoxicity of Cyproheptadine and Methysergide to Chemically Induced Carcinomas of Rat Colon.** (Eng) Barkla, D. H. (Dept. Anatomy, Monash Univ., Clayton, Victoria 3168, Australia); Tutton, P. J. *Br J Cancer* 36(6): 814-819; 1977.

The effect of ip cyproheptadine (1 mg/kg) or methysergide (0.1 mg/kg) on 1,2-dimethylhydrazine-induced colonic tumors in male Sprague-Dawley rats was investigated. The animals were killed 15 hr after ip injection. Approx 30% and 25% tumor necrosis was observed in the methysergide- and cyproheptadine-treated animals, respectively, compared to 9% in controls. Electron microscopy observations suggest that these compounds induce changes in the tumor cell membranes: discontinuities and dilations were noted in the lateral plasma membranes, nuclear membranes, and mitochondria. Similar changes were occasionally seen in untreated animals with tumors > 1 cm in diameter. Since similar results have been observed with other 5-hydroxytryptamine (5HT)-related compounds, it is suggested that these compounds may have a role in the chemotherapy of colonic tumors. (8 refs.)

78-0246 **The Possible Role of Nucleic Acid Alkylation in the Organ Specificity of Carcinogens.** (Eng) Montesano, R. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, Lyon, France); Margison, G. P.; Likhachev, A. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 221-231; 1977.



The significance of the formation of O<sup>6</sup>-methylguanine (O-MEG) and 7-methylguanine (7-MEG) in DNA during carcinogenesis was investigated in various animals. A single sc dose of 300 mg/kg 1,2-dimethylhydrazine (DMH) was given to rats. The highest 7-MEG levels were found in liver DNA after 3 hr, but 7-MEG was also detected in the mucosa of the colon, kidney, testes, lung, and ileum; these levels decreased by 72 hr. O-MEG was found in the liver and colon DNA, with the amount in the latter being four times that of the former. Thus, O-MEG appears to persist in organs in which tumors are induced. Syrian golden hamsters administered 25 mg/kg dimethylnitrosamine (DMN) had 1.5 times more alkylation of liver DNA than BD-IV rats treated similarly. However, the difference in the incidence of liver tumors did not correlate with differences in initial levels of 7-MEG or O-MEG. Rat liver enzymatically excised O-MEG from its DNA with high efficiency but hamster liver did not. 7-MEG was lost more rapidly from hamster liver DNA than from rat liver DNA, suggesting that this excision may be an active process. These findings suggest that O-MEG plays an important role in the induction of tumors by alkylating agents. BD-IV rats received 0.0025% DMN in the drinking water 5 days/wk for 8.5 wk followed by 10 mg/kg N-methyl-N-nitrosourea iv. O-MEG excision from liver DNA was not reduced during chronic DMN administration and thus is not a major factor in the induction of liver tumors in rats on this schedule. Administration of labeled DMN (2 mg/kg/day, 5 days/wk) for 2, 4, 8, 16, and 24 wk did not lead to an accumulation of O-MEG in target organ DNA. Thus, chronic administration of DMN has no effect on the rate of removal of O-MEG from liver DNA. (31 refs.)

**78-0247 Investigations into the Metabolism and Mode of Action of the Colon Carcinogens 1,2-Dimethylhydrazine and Azoxymethane.** (Eng) Fiala, E. S. (American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY 10595). *Cancer [Suppl]* 40(5): 2436-2445; 1977.

Previous work on the metabolism of the colon carcinogen 1,2-dimethylhydrazine and its inhibition by disulfiram, carbon disulfide, and other thionosulfur compounds is summarized. Ongoing studies with <sup>14</sup>C-labeled azoxymethane (AOM) indicate that in male F-344 rats, this colon carcinogen is rapidly metabolized to <sup>14</sup>CO<sub>2</sub> (37%, 48 hr) and to <sup>14</sup>C-methylazoxymethanol (MAM:0.6%-1%), which, along with other metabolites, appears in the urine. Pretreatment of rats with phenobarbital or chrysene increases exhaled <sup>14</sup>CO<sub>2</sub> to 53% and 65%, respectively. Pretreatment with disulfiram or CS<sub>2</sub> decreased urinary MAM, and increases unmetabolized AOM levels in the exhaled air and in urine significantly. Thus, phenobarbital and chrysene stimulate but disulfiram and CS<sub>2</sub> inhibit the metabolism of AOM. In vitro hydroxylation of AOM to MAM was demonstrated with rat liver homogenates and microsomal fractions. A hypothetical scheme for the endogenous formation of AOM is presented. (30 refs.)

**78-0248 Colonic Neoplasms in Mice Produced with Six Injections of 1,2-Dimethylhydrazine.** (Eng) Deschner, E. E. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Long, F. C. *Oncology* 34(6): 255-257; 1977.

A new method of inducing colonic neoplasms is presented in which female CF<sub>1</sub> mice were given six weekly injections of dimethylhydrazine (DMH: 20 mg/kg/wk sc). Six mice were sacrificed starting 20 wk after the initial injection and continuing every 3-5 wk up to the 45th. None of the controls had gastrointestinal tumors. Of the 43 treated mice that survived to autopsy (weeks 20-45), 83% had visible colonic neoplasms with a frequency of 2.1 tumors per animal. Most tumors (61%) were found in the 3-cm segment of the large bowel above the anus; none were seen in the duodenum or other portions of the small intestine. Thirteen treated mice had carpeting of the large bowel or uncountable numbers of tumors. Carpeting was most evident in the 3 cm above the anus. Ten of these mice also had isolated tumors in the remainder of the bowel. Rectal bleeding, when present, was associated with tumor appearance, but it did not consistently accompany tumor formation. Marked thickening of the bowel wall, characterized by local atypia and zones of dysplasia, and extreme thinning, characterized by mucosal atrophy, were also noted after DMH treatment. (20 refs.)

**78-0249 Influence of Gonadal Hormones and Age on 1,2-Dimethylhydrazine-induced Colon Carcinogenesis.** (Eng) Moon, R. C. (Life Sciences Div., IIT Res. Inst., 10 W. 35th St., Chicago, IL); Fricks, C. M. *Cancer [Suppl]* 40(5): 2502-2508; 1977.

BD-II and BD-IX male and female rats received weekly sc injections of 15 mg/kg 1,2-dimethylhydrazine dihydrochloride (DMH), beginning at 35, 120, or 210 days of age and continuing for 20 wk. Control animals received only the DMH vehicle. Additional BD-II and BD-IX male and female rats of the three age groups were gonadectomized at 21, 106, and 196 days. Beginning 14 days after gonadectomy, the rats received 15 mg/kg DMH sc once a week for 20 wk. The animals were sacrificed 35 wk after the initial DMH injection. Control rats of the appropriate age and sex did not develop colon tumors. BD-IX rats appeared to be more sensitive to colon cancer induction by DMH than BD-II rats. The cancer incidence was less in females than in males in both the BD-II and BD-IX animals. Gonadectomy did not affect the incidence in BD-II males or females or in the BD-IX females, but it reduced the incidence in BD-IX males exposed initially at either 120 or 210 days. The administration of androgen to castrate BD-IX males (120-day-old group) increased the colon cancer incidence to a level approaching that in intact animals, but it had little effect in the BD-II castrate males. These data suggest a genetically influenced susceptibility to DMH-induced colon carcinogenesis between BD-II and BD-IX rats. Furthermore, a sex difference is evident in both BD lines, but age appears to be a factor only in older BD-IX



females. Apparently, androgens influence DMH-induced tumorigenesis in BD-IX males only if the initial exposure of DMH occurs after sexual maturity. (22 refs.)

- 78-0250 **Alterations in Fecal Microflora Enzymes Related to Diet, Age, Lactobacillus Supplements, and Dimethylhydrazine.** (Eng) Goldin, B. (Infectious Disease Service, New England Medical Center, 171 Harrison Ave., Boston, MA 02111); Gorbach, S. L. *Cancer (Suppl)* 40(5): 2421-2426; 1977.

The bacterial enzymes  $\beta$ -glucuronidase, azoreductase, and nitroreductase were measured in the fecal microflora of Fischer rats. The effects of diet, advanced age, *Lactobacillus acidophilus* supplements, and dimethylhydrazine (DMH: 20 mg/kg/wk, sc) on these microbial enzyme activities were determined. The shift from a grain to a meat diet resulted in a 1.5- to 2.5-fold increase in the activity of all three enzymes. Animals > 20 mo of age on a meat diet showed further increases in fecal  $\beta$ -glucuronidase activity, but the levels of all three microbial enzymes increased in old rats fed a grain diet. Feeding supplements of *L. acidophilus* significantly lowered fecal nitroreductase and azoreductase activity in meat-eating animals; but it had no effect on nitroreductase activity in grain-fed animals. DMH increased the fecal  $\beta$ -glucuronidase activity in both grain- and meat-fed animals, but the carcinogen had no effect on nitroreductase or azoreductase activity. These findings have relevance to known features of the epidemiology and etiology of large bowel cancer, and they suggest certain approaches to prevention. (25 refs.)

- 78-0251 **Experiments on the Influence of an Aromatic Retinoid on the Chemical Carcinogenesis in Rats by Butyl-butanol-nitrosamine and 1,2-Dimethylhydrazine.** (Eng) Schmahl, D. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Habs, M. *Arzneim Forsch* 28(1): 49-51; 1978.

The effect of ethylallyl-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6, 8-nonatetraenoate (Ro 10-9359) on butylbutanolnitrosamine (BBN)-induced bladder cancers and 1,2-dimethylhydrazine (DMH)-induced colon cancers in rats was investigated. Male Sprague-Dawley rats were divided into two groups: one received BBN (10 mg/kg/day in the drinking water) and one received DMH (10 mg/kg/wk sc). Ro 10-9359 was administered po three times a wk in doses of 8, 16, and 32 mg/kg. Applications of the highest dose were occasionally interrupted because of A-hypervitaminosis. Neither an enhancing nor an inhibitory tumor effect was observed with any dose of Ro 10-9359. (30 refs.)

- 78-0252 **Quantitative Determination of Hydrazines Derived from Isoniazid in Man.** (Eng) Iguchi,

S. (Faculty Pharmaceutical Sciences, Kyushu Univ., Fukuoka 812, Japan); Goromaru, T.; Matsuyama, K.; Sogabe, K. *Chem Pharm Bull (Tokyo)* 25(10): 2796-2800; 1977.

The amount of free hydrazine excreted in human urine after po isoniazid (INH) administration was quantitated by mass fragmentography using  $^{15}\text{N}$ -hydrazine as the internal standard. Unchanged INH, acetyl-INH, monoacetylhydrazine, and diacetylhydrazine were analyzed simultaneously. Representative analytical data are tabulated. (20 refs.)

- 78-0253 **An Assessment of the Possible Association of Isoniazid with Human Cancer Deaths.** (Eng) Glassroth, J. L. (Res. and Development Branch, Tuberculosis Control Div., Center Disease Control, Atlanta, GA 30333); White, M. C.; Snider, D. E. *Am Rev Respir Dis* 116(6): 1065-1074; 1977.

Data from two trials of the use of isoniazid for the prevention and therapy of tuberculosis, each of which included > 25,000 persons, were reviewed to evaluate the risk of death from cancer among persons who received this treatment. In each trial, patients were randomly assigned to isoniazid or a placebo. The length of follow-up was 10-14 yr in one trial and 9-11 yr in the other. Comparisons were made of crude and age-adjusted cancer death rates, of annual cancer death rates, and of the Adapted International Classification of Disease (ICDA) categories for specific malignancies. No significant difference in the incidence of death from cancer was noted between groups treated with placebo or with isoniazid, even when deaths due to specific types of cancer and age-specific cancer death rates were compared. In view of the long latent period between exposure to a carcinogen and the appearance of some types of cancer, it is impossible to conclude that isoniazid is not a carcinogen, but the results agree with other studies that have found no evidence of a carcinogen effect of isoniazid in humans. (24 refs.)

- 78-0254 **Quinoline: Conversion to a Mutagen by Human and Rodent Liver.** (Eng) Hollstein, M. (Dept. Environmental Health Sciences, Sch. Public Health, Univ. California, Berkeley, CA 94720); Talcott, R.; Wei, E. *J Natl Cancer Inst* 60(2): 405-410; 1977.

Quinoline, a rat hepatocarcinogen, and 23 quinoline derivatives were tested for mutagenic activity in Ames *Salmonella typhimurium* assay. Quinoline, 5-hydroxyquinoline, and 8-hydroxyquinoline were mutagenic in strain TA 100 when Aroclor 1254-induced rat (male outbred Sprague-Dawley) liver homogenate was present in the incubation mixture. Enzyme preparations from rats pretreated with P-448-dependent aryl hydrocarbon hydroxylase inducers [3-methylcholanthrene (3-MC) and  $\beta$ -naphthoflavone] and 3-MC-treated "responsive" C57BL mice also metabolized quinoline to a mutagen, but phenobarbital and pregnenolone-16 $\alpha$ -carbonitrile pretreatment did not yield active prepara-



tions. The mutagenicity of quinoline was inhibited in vitro by menadione, butylated hydroxytoluene,  $\alpha$ -naphthoflavone vitamin A acetate, and glutathione. Depletion of glutathione by diethylmaleate pretreatment in vivo enhanced the mutagenic potential of the liver enzyme preparation. Mutagenic activity correlated with the formation of water-soluble quinoline metabolites, and the reactive quinoline intermediate quinoline-2,3-epoxide. Microsomal enzymes isolated from human liver tissue, but not lung tissue, also activated quinoline to a mutagen. (23 refs.)

- 78-0255 Radiation-induced Binding of 4-Nitroquinoline-N-Oxide to DNA in Aqueous Solution.** (Eng) Yamamoto, O. (Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima, Japan); Gholi-pour-Khalili, I. *J Radiat Res* 18(3): 194-199; 1977.

The binding of 4-nitroquinoline N-oxide (4-NQO) to single and double-stranded calf thymus DNA was investigated after irradiation of the solution with 60  $\gamma$  rays and compared to that of cysteine. Curves of dose vs binding of cysteine to single and double-stranded DNA and of 4-NQO to double-stranded DNA followed first-order kinetics. Binding of 4-NQO to single-stranded DNA was a second-power function of radiation dose. (8 refs.)

- 78-0256 Carcinoma of the Nasal Mucosa Following Occupational Exposure to Chromate.** (Ger) Muller, C. (Bezirksinspektion Gesundheitsschutz in den Betrieben Leipzig, Bruhl 42-50, DDR-701 Leipzig, E. Germany); Wiezorek, W. D. *Dtsch Gesundheitsw* 32(36): 1716-1717; 1977.

A 65-yr-old man developed squamous epithelial carcinoma of the nasal mucosa after 50 yr exposure to chromates in the chromium industry. He had been working as a polisher during the first 21 yr and as a chromium plater thereafter. (no refs.)

- 78-0257 Effects of Potassium Dichromate on Nucleic Acid and Protein Syntheses and on Precursor Uptake in BHK Fibroblasts.** (Eng) Levis, A. G. (Inst. Animal Biology, Univ. Padua, Via Loredan 10, 35100 Padua, Italy); Buttignol, M.; Bianchi, V.; Sponza, G. *Cancer Res* 38(1): 110-116; 1978.

To elucidate the mechanisms of chromium cytotoxicity, potassium dichromate effects on nucleic acid and protein metabolism were studied in baby hamster kidney (BHK) fibroblasts grown in vitro. Treatment of the cells with  $10^{-4}$  M potassium dichromate for 1-4 hr reduced DNA and RNA accumulation rates in BHK fibroblasts, as determined by quantitative spectrophotometry. The inhibitory action was

not immediately evident on the basis of the incorporation rates of labeled nucleosides into DNA and RNA, as the dichromate also affects the relative concentrations of labeled precursors in the intracellular pool. Nucleoside (mostly thymidine) uptake was first stimulated by dichromate and then inhibited, whereas amino acid uptake was immediately inhibited. Actual rates of macromolecular syntheses were calculated by taking into account the induced changes of soluble precursor concentrations. These normalized rates indicate that dichromate induces a sudden blockage of DNA replication but that RNA and protein syntheses are inhibited secondarily. Such a pattern could be due to a differential action of dichromate on the enzymes involved in nucleic acid and protein syntheses. On the basis of the curves of BHK survival to potassium dichromate and of physicochemical studies of DNA treated in vitro with trivalent and hexavalent chromium, it is suggested that the final effect of dichromate is a stabilization of the DNA molecule, which could also account for the differential inhibition of macromolecular syntheses. (31 refs.)

- 78-0258 Report on Bioassay of Dapsone for Possible Carcinogenicity.** (Eng) Frederickson, D. S. (NIH, Bethesda, MD 20014). *Fed Regist* 42(234): 61631-61632; 1977.

The carcinogenicity of dapsone (4,4'-sulfonyldianiline) to male and female Fischer 344 rats (600 or 1,200 ppm dapsone in the diet) was determined. Mesenchymal tumors were noted in the abdominal or peritoneal organs in 13/35 low-dose and 22/33 high-dose male rats. This incidence was significant compared to pooled controls. There were no tumors in female rats or mice that could be linked to treatment. (no refs.)

- 78-0259 Studies of the Tumorigenic Effect of Two Goitrogens.** (Eng) Jemec, B. (Fibiger Lab., Ndr. Frhavnsgeade 70, DK-2100 Copenhagen O, Denmark). *Cancer* 40(5): 2188-2202; 1977.

The nature of thyroid gland and lung tumors arising in C3H mice fed the goitrogens methylthiouracil (MTU: 0.2%-0.5%) and 1-methyl-1-mercaptoimidazol (MMI: 35-500 mg/liter drinking water) was studied. Both drugs significantly increased the incidence of thyroid neoplasms in mice on an iodine-deficient diet, but the effect of MTU was greater than that of MMI. The adenomas appeared within 5-7 mo of treatment, and in 16 mice their development was accompanied by the appearance of pulmonary nodules. There was also a significant increase in hepatoma incidence in the MTU-treated animals. Although the thyroid adenomas disappeared after MTU was withdrawn, pulmonary nodules were found in mice in whom thyroid enlargement persisted for 6 mo after treatment was discontinued. Histologic studies showed that these nodules were emboli from hyperplastic thyroid tissue. (39 refs.)



**78-0260 Suppressive Effect of Copper on Ethylation of Rat Liver DNA with Ethionine In Vivo.** (Eng) Yamane, Y. (Faculty Pharmaceutical Sciences, Chiba Univ., 1-33, Yayoi-cho, Chiba 280, Japan); Sakai, K.; Shibata, M.; Chiba, K. *Gann* 68(5): 713; 1977.

Treatment of rats with 0.25% or 0.5% basic cupric acetate suppressed ethionine ethylation of their liver DNA by 38% and 46%, respectively. With the 0.5% preparation, the accumulation of copper was 218.8  $\mu\text{g/g}$  in the whole liver, 134.4  $\mu\text{g/g}$  in the 600 x g pellet, 48.3  $\mu\text{g/g}$  in the nuclear fraction, and 0.079  $\mu\text{g/mg}$  DNA in the DNA. (6 refs.)

**78-0261 II-III Translocations Induced by Diethyl Sulfate in Mature Sperm of *Drosophila melanogaster*.** (Eng) Munoz, E. R. (Departamento de Radiobiologia, Comision Nacional de Energia Atomica, 1429 Buenos Aires, Argentina); Barnett, B. M. *Mutat Res* 45(3): 355-357; 1977.

Male *Drosophila melanogaster* were exposed to a 0.5% solution of diethyl sulfate (DES) for 3.5 hr or to a 0.75% solution for 2.5 hr and mated to examine II-III translocations. A sex-linked recessive lethal test was run with some of the males treated with the 0.5% solution, and the frequency of lethals was 138/509. With the 0.5% DES treatment, no II-III translocations were observed until the fifth subculture (16-18 days), when an incidence of 22/969 was observed. This incidence increased to 7/120 at 23-29 days. With the 0.75% DES solution, the incidence of translocations was 1/334 after 6-8 days and 14/178 by 23-29 days. It is concluded that DES is an efficient chromosome breaker. Since translocations were not detected without storage, it is suggested that the time interval between treatment and union of pronuclei after fertilization is not sufficient to allow lesions to develop into actual breaks and exchange fragments. (12 refs.)

**78-0262 Hair Dyes and Bladder Cancer (Letter to Editor).** (Eng) Jain, M. (Epidemiology Unit, Natl. Cancer Inst., Toronto, Ontario, Canada); Morgan, R. W.; Milson, L. *Can Med Assoc J* 117(10): 1131,1133; 1977.

No significant difference in exposure to hair dyes was found between 107 patients with transitional cell carcinoma of the bladder and 107 age- and sex-matched controls. For those using hair dyes, the relative bladder cancer risk estimate of 1 had a 95% confidence limit of 0.41-3.03. (12 refs.)

**78-0263 Bromocriptine and Uterine Neoplasia (Letter to Editor).** (Eng) Griffith, R. W. (Biological and Medical Res., Sandoz Ltd., Basel, Switzerland). *Br Med J* (6102): 1605; 1977.

The effect of 1.7, 9.8 and 44 mg/kg/day bromocriptine on rats was investigated. At the low dose, inflammatory, hyper-

plastic, and metaplastic changes in the uterus were increased, but the number of tumors in females was significantly reduced. At the middle and high doses, there was a decreased tumor incidence in both sexes, but an increase in uterine neoplasia in females. Since bromocriptine reduces pseudopregnancy in rats by a prolactin inhibiting action, the formation of vaginal cornification is favored. Differences in the effects of aging on reproductive function in humans prevent similar changes, but women on this therapy should have regular gynecologic evaluation. (no refs.)

**78-0264 In Vitro Transformation of Hamster Embryo Cells with Tryptophan Pyrolysis Products.** (Eng) Takayama, S. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Katoh, Y.; Tanaka, M.; Nagao, M.; Wakabayashi, K.; Sugimura, T. *Proc Jpn Acad* 53(3): 126-129; 1977.

The transformation potential of the two basic fractions of D,L-tryptophan pyrolyzate, Trp-P-1, and Trp-P-2, were investigated using cryopreserved primary cultures of Syrian golden hamster embryo cells as both target and feeder layer cells. The cultures were incubated with varying concentrations of the pyrolyzate for 8 days, stained, and examined. Cultures treated with 0.1  $\mu\text{g}$  Trp-P-1 were transformed 0.49%, those treated with 0.5  $\mu\text{g}$ , 1.35% and those treated with 1.0  $\mu\text{g}$ , 0%. Cultures treated with 0.1  $\mu\text{g}$  Trp-P-2 were transformed 0.59%, those treated with 0.5  $\mu\text{g}$ , 1.53%, and those treated with 1.0  $\mu\text{g}$ , 0%. Thus, Trp-P-2 was less toxic. Treatment of cells with 5  $\mu\text{g}$  of the entire fraction of tryptophan pyrolyzate resulted in 0.18% transformation that increased to 0.57% with 10  $\mu\text{g}$ ; 0% transformation was observed with 25  $\mu\text{g}$ . The transformed cultures had a random-oriented growth pattern, with the more-basophilic cells accumulating in the center of the colonies. The in vivo carcinogenicity of these fractions is being investigated. (8 refs.)

**78-0265 The Influence of Diet on the Growth of Streptozotocin-induced Renal Tumours in Sprague-Dawley Rats.** (Eng) Hartig, F. (Boehringer Mannheim GmbH, W. Germany); Hebold, G. *IRCS Med Sci: Cancer* 5(11): 530; 1977.

The effect of diet on the formation of renal tumors in streptozotocin diabetic male Sprague-Dawley rats was investigated. Diabetes was induced with 65 mg/kg streptozotocin sc. After 11 days, the animals were fed a diet containing (1) 50% carbohydrate, 15% protein, 2% fat; (2) 6% carbohydrate, 50% protein, 15% fat; or (3) 5% carbohydrate, 27% protein, 42% fat. The tumor incidence for the three groups was 0/14, 5/11, and 2/14, respectively, with Group 2 being statistically significant. The diabetic state was improved in Group 2 animals, but they also had more marked glomerulopathies and changes in their renal parenchyma. (5 refs.)

**78-0266 Streptozotocin-induced Renal Tumours in Rats.** (Eng) Horton, L. (Dept. Surgical Pathology, St.



Thomas's Hosp. Medical Sch., London SE1 7EH, England); Fox, C.; Corrin, B.; Sonksen, P. H. *Br J Cancer* 36(6): 692-699; 1977.

Renal tumors developed in 36/80 male Wistar rats with streptozotocin-induced diabetes (single iv dose of 25 mg/kg). Although no metastases were noted, some of the tumors penetrated the renal capsule and were locally invasive. There were 14 epithelial tumors in 13 rats and 32 mesenchymal tumors. The former resembled human renal adenomas and adenocarcinomas and the latter resembled nephroblastomas. Treatment of the diabetes did not influence tumor incidence, but insulin-treated animals had a higher mortality than untreated animals or those given a low-carbohydrate diet. (31 refs.)

**78-0267 In Vitro Transformation of Hamster Embryo Cells by Quercetin.** (Eng) Umezawa, K. (Dept. Molecular Oncology, Inst. Medical Science, Univ. Tokyo, Shirogane-dai, Minato-ku, Tokyo 108, Japan); Matsushima, T.; Sugimura, T.; Hirakawa, T.; Tanaka, M.; Katoh, Y.; Takayama, S. *Toxicol Lett* 1(3): 175-178; 1977.

The in vitro carcinogenic activities of bracken extract and two flavone derivatives, kaempferol and quercetin, were examined in a transformation assay with cryopreserved hamster embryo cells. Bracken extract and kaempferol did not induce transformation, but quercetin induced morphological transformation at concentrations of 5 and 10 µg/ml. (10 refs.)

**78-0268 Mutagenicity of the Triazine Herbicides Atrazine, Cyanazine, and Simazine in *Drosophila melanogaster*.** (Eng) Murnik, M. R. (Dept. Biological Sciences, Western Illinois Univ., Macomb, IL 61455); Nash, C. L. *J Toxicol Environ Health* 3(4): 691-697; 1977.

Assays for dominant lethal mutations, sex-linked recessive lethal mutations, and chromosome breakage, nondisjunction, and loss were performed on *Drosophila melanogaster* males treated by injection or by larval feeding of the herbicides atrazine (2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine), cyanazine [2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-1,3,5-triazine], or simazine [2-chloro-4,6-bis-(ethylamino)-1,3,5-triazine]. The three herbicides significantly increased the rate of apparent dominant lethals, but this reduction in egg hatch was probably due to physiologic toxicity to sperm. Atrazine significantly increased X-linked recessive lethals and X or Y loss after treatment by larval feeding. Injection of simazine elevated X-linked lethals, but larval feeding did not. None of the herbicides significantly increased partial loss of the Y chromosome or sex chromosome nondisjunction. Much larger experiments are needed to determine the mutagenic potential of these herbicides conclusively. (23 refs.)

**78-0269 Carcinogen-induced Chromosome Breakage in Fanconi's Anemia Heterozygote Cells (Meeting Abstract).** (Eng) Auerbach, A. D. (New York Univ. Sch. Medicine, New York, NY); Wolman, S. R. *Am J Hum Genet* 29(6): 20A; 1977. (no refs.)

**78-0270 Mutagenicity and Biotransformation Studies with Nitrofurans (Meeting Abstract).** (Eng) Goodman, D. R. (Univ. California, San Francisco, CA). *Dis Abstr Int (B)* 38(6): 2632-B-2633-B; 1977. (no refs.)

**78-0271 Experimental Carcinogenesis of Pyrolysis Fuel Oil.** (Eng) Weil, C. S. (Carnegie-Mellon Inst. Res., Carnegie-Mellon Univ., Pittsburgh, PA 15215); Condra, N. I. *Am Ind Hyg Assoc J* 38(12): 730-733; 1977.

The carcinogenicity of both water- and oil-quench pyrolysis fuel oils was examined by the application of one brushful of the oils to the shaved midline skin of C3H/HeJ mice three times per week for life. Control mice received either water or benzene; no tumors were noted in these animals. Of mice treated with water-quench fuel oils, 36 developed papillomas and 35 developed carcinomas for indices of 100.0 and 97.2, respectively. The median latent periods for the two tumor types were 10.2 and 12.2 mo, respectively. With the oil-quench fuel oils, 35 mice had papillomas and 34 had carcinomas for an index of 94.4 each. The latent periods were 10.3 and 12.1 mo, respectively. All the malignant tumors were diagnosed as squamous carcinomas. Four of the water-quench group and five of the oil-quench group had metastases to the lung. Three of the latter also had metastases to the thoracic cavity. These findings should serve as a warning of a possible health hazard to humans. (5 refs.)

**78-0272 Adrenal Carcinoma in Child with History of Fetal Alcohol Syndrome (Letter to Editor)** (Eng) Hornstein, L. (Univ. Affiliated Cincinnati Center Developmental Disorders, Dept. Pediatrics, Univ. Cincinnati, Cincinnati, OH 45229); Crowe, C.; Gruppo, R. *Lancet* 2(8051): 1292-1293; 1977.

A 13-yr-old girl with fetal alcohol syndrome developed a nonsecreting adrenal cortical carcinoma that metastasized to the bone, lungs, liver, abdominal nodes, and bone marrow. It is possible that the alcohol syndrome was responsible for tumor development or that a genetic mechanism (a paternal uncle had a cerebral astrocytoma) was involved. (10 refs.)



8-0273 **Arginase Activity and Other Cellular Events Associated with Epidermal Hyperplasia.** (Eng) Edmond, A. F. (Dept. Dermatology, Medical Coll. Virginia, C.U., Richmond, VA 23298); Rothberg, S. *J Cell Physiol* (1): 99-104; 1978.

The sequence of cellular events associated with the induction of epidermal hyperplasia in male hairless mice (hr/hr) following two 0.2 ml application of 1-decanol 1 hr apart was studied. Six hours after the first application, histological identification of the basal cells is difficult; incorporation of labeled thymidine into epidermal DNA is inhibited by 60%-80%. By day 2, epidermal scales have desquamated and a new hyperplastic epidermis is evident. Although on day 1 DNA content is 5%-40% of control levels, incorporation of thymidine is elevated 70%-170% and this is increased to 110-310% on day 2. Epidermal arginase is at control levels on day 1 and increases to 45%-165% above control levels by day 2. By day 3 thymidine incorporation is elevated by 40%-120% but falls to control levels by day 4. Concurrently, epidermal DNA content and protein content are increased 5%-105% and 5%-90% above controls, respectively. Arginase activity was 5%-630% above controls on day 3 and although this level varied on days 4-7, it was always elevated when there was histological evidence of hyperplasia. These results are discussed in terms of polyamine synthesis and other metabolic events. (20 refs.)

*See also:*

\*(Rev.): 78-0001, 78-0002, 78-0003, 78-0004, 78-0005, 78-0006, 78-0007, 78-0008, 78-0013, 78-0016, 78-0017, 78-0018, 78-0019, 78-0020, 78-0021, 78-0022, 78-0023, 78-0024, 78-0025, 78-0026, 78-0027, 78-0028, 78-0029, 78-0030, 78-0031, 78-0032, 78-0033, 78-0034, 78-0035, 78-0036, 78-0037, 78-0038, 78-0039, 78-0040, 78-0041, 78-0042, 78-0043, 78-0044, 78-0045, 78-0046, 78-0047, 78-0048, 78-0049, 78-0050, 78-0051, 78-0052, 78-0053, 78-0054, 78-0055, 78-0056, 78-0057, 78-0058, 78-0059, 78-0060, 78-0061, 78-0062, 78-0063, 78-0064, 78-0065, 78-0066, 78-0067, 78-0072, 78-0102, 78-0108, 78-0109.

\*(Phys.): 78-0282, 78-0385.

\*(Viral): 78-0406.

\*(Immun.): 78-0424, 78-0426, 78-0431, 78-0433, 78-0444, 78-0449, 78-0451, 78-0452, 78-0453.

\*(Path.): 78-0461, 78-0463, 78-0470, 78-0473, 78-0489, 78-0492, 78-0496, 78-0501, 78-0502, 78-0510, 78-0511, 78-0513, 78-0514, 78-0533, 78-0535, 78-0536, 78-0541.

\*(Epid.-Biom.): 78-0550, 78-0561, 78-0564, 78-0565, 78-0567, 78-0575, 78-0580, 78-0582.



## PHYSICAL CARCINOGENESIS

- 78-0274 **Cellular Attachment to Implanted Foreign Bodies in Relation to Tumorigenesis.** (Eng) Ferguson, D. J. (Dept. Surgery, Univ. Chicago, Chicago, IL 60637). *Cancer Res* 37(12): 4367-4371; 1977.

Experiments demonstrating that the tumorigenicity of implanted plastic films decreased with an increase in surface roughness or pore size were repeated to examine cellular attachment to these objects and to filters strengthened and made impermeable by bonding to plastic. Round 13-mm disks of methyl methacrylate implanted sc in A/BiF/F50+ mice produced sarcomas in 12% of the mice at 64 wk. Tumor incidence increased to 60% in mice receiving disks to which cellulose filters with pore sizes of 0.025 to 0.1  $\mu$ m were bonded. However, no tumors occurred with disks covered by 0.45- $\mu$ m filters and followed up to 83 wk. Vinyl coverslips 15 mm square also produced no sarcomas when covered by 0.5- $\mu$ m filters; plain vinyl produced sarcomas in 40% of mice at 64 wk. Sanding of the vinyl surfaces reduced tumorigenicity to 11%. Permeability, fragility, and storage capacity of the filters are apparently not related to tumorigenicity. Surface roughness probably is related. Cells, mostly macrophages, were densely and uniformly attached to the nontumorigenic surfaces from 24 hr to 2 yr after implantation, but they were distinctly fewer and not uniformly distributed on the tumorigenic surfaces. Topology favoring attachment was inherent in the 0.450- $\mu$ m filters, and it was produced in the plastic by gouging irregular excavations 10 to 15  $\mu$ m deep. (9 refs.)

- 78-0275 **Neutron Carcinogenesis: Dose and Dose-Rate Effects in BALB/c Mice.** (Eng) Ullrich, R. L. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Jernigan, M. C.; Storer, J. B. *Radiat Res* 72(3): 487-498; 1977.

The influence of dose and dose rate on the tumorigenicity of neutrons was investigated in female BALB/c mice exposed to various neutrons doses at rates of 5 and 25 rads/min and 1 rad/day. The tumors that were most sensitive to induction after neutron exposures included malignant lung adenocarcinomas, mammary adenocarcinomas, and ovarian tumors. For these three types, increased incidences were observed after as little as 5-10 rads of neutrons delivered at high dose rate (HDR). After low-dose-rate (LDR) neutron exposures, however, different dose-response relationships were observed. Neutron irradiation at a LDR was less effective than that at a HDR in inducing ovarian tumors at all doses tested. For malignant lung and mammary tumors, the data suggested that the LDR was less effective than the HDR at low total doses, but it was more effective at high total doses. The data are not sufficient to establish the mechanistic basis for the

dose-response relationship observed for lung and mammary tumors, but it is clear that these relationships can vary as a function of both total dose and dose rate. Factors such as intercellular recovery, immune competence, hormonal balance, and changes in the kinetics of target and interacting cell populations may be modified by dose rate and may play a modifying role in carcinogenesis. (12 refs.)

- 78-0276 **Reevaluation of the Number of Cells Involved in the Neutron Induction of Mammary Neoplasms.** (Eng) Gould, M. N. (Argonne Natl. Lab., Div. Biological and Medical Res., 9700 S. Cass Ave., Argonne, IL); Jirtle, R.; Crowley, J.; Clifton, K. H. *Cancer Res* 38(1): 189-192; 1978.

The question of the number of cells involved in the neutron induction of mammary neoplasms was reevaluated in view of conflicting conclusions from previous analyses. The shape of the curve relating carcinogen dose to the number of animals developing neoplasms was reexamined. A family of curves relating expected tumor incidence to carcinogen dose, if tumors arose from one cell or two or more interacting cells, was calculated. The degree of correspondence of these curves to reported radiation dose in relation to mammary tumor incidence in Sprague-Dawley rats was then determined. The results do not agree with the conclusion that mammary tumor induction in Sprague-Dawley rats depends on the action of neutron radiation on more than one cell. Although the analysis shows that the data are well fit by a one-cell-origin model, it is not suggested that the single-cell origin of these tumors is proved but that a working hypothesis of the single-cell origin is the simplest logical choice. (7 refs.)

- 78-0277 **Quantitative Analysis of Thymus Lymphoid Cells During Murine Radioleukemogenesis.** (Eng) Boniver, J. (Lab. Morbid Anatomy, Inst. Pathology, State Univ. Liege, Sart Tilman, 4000 Liege, Belgium); Simar, L. J.; Courtoy, R.; Betz, E. H. *Cancer Res* 38(1): 52-58; 1978.

Changes in the thymus blast population of C57BL mice subjected to four whole-body irradiations of 150 R at 8-day intervals were determined. After each dose, the subcapsular zone showed a lymphoid cell depletion, followed by a regenerative phase with a return of blast cells to normal values. However, after the last dose, the number of small lymphocytes did not return to normal as quickly, giving the appearance that blasts accumulated in the subcapsular zone. Lymphoblasts predominated in the irradiated animals, but the percentage of X-cells increased during each regenerative phase, reaching



about 50% after the last fraction. The frequency of ring-shaped nucleoli cells (RSN) was relatively unaffected. By 90 days, 65% of the thymuses of irradiated animals were identical to controls and 35% were atrophic. The atrophic thymuses were characterized by lymphocytic depletion of the subcapsular zone and a high numerical density of blast cells. The percentage of RSN was higher than in controls and irradiated nonatrophic thymuses, but the absolute number of these and other blast cells was not significantly higher than control values. During leukemogenesis, the surface density of the Golgi membranes diminished in lymphoblasts of nonatrophic and lymphomatous thymuses, in RSN, and, to a lesser extent, in X-cells of atrophic and lymphomatous thymuses. (3 refs.)

78-0278 **Leukemia and Lymphoma in Irradiated Parabiont Rats.** (Eng) Warren, S. (Cancer Res. Inst., New England Deaconess Hosp., Boston, MA 02215); Chute, C. N.; Porter, M. W.; Brown, C. E.; Gates, O. *Radiat Res* 88(3): 512-518; 1977.

The effects of high-dose whole-body x-radiation (1,000 R) to one of a pair of parabiosed NEDH rats on the incidence of leukemia and lymphoid tumors were investigated. Leukemia and lymphoid tumors each have a 2% spontaneous rate in NEDH rats. Parabiosis alone increased in incidence of these malignancies to 5%. Radiation did not increase the incidence of leukemia or lymphoid tumors significantly in either partner, and it sharply decreased the incidence of lymphosarcoma in female pairs. The monocytoid and myeloid leukemias were the more common types. Leukemia was often but not always shared by both partners. The solid lymphoid tumors were usually restricted to one partner. Their incidence rates did not differ significantly between the irradiated and shielded partners: the occurrence of lymphosarcoma was 0.3% and 0.5% respectively, that of reticulum cell sarcoma 1.1% and 1.5%, respectively. These results indicate that exposure to 1,000 R dose not increase the incidence of leukemia and solid lymphoid tumors in the irradiated partners and may even inhibit it somewhat, probably because of a killing of cells susceptible to neoplastic alteration. The findings also suggest that the radiation effect in the rat is complex and not the summation of simple dose-effect relationships for each cell type exposed. (16 refs.)

78-0279 **Histogenesis of Radiation-induced Intestinal Tumors (Meeting Abstract).** (Eng) Stinson, W. (Dept. Anatomy, Univ. Nebraska Medical Center, Omaha, NB); Sharp, J. G.; Osborne, J. W. *Anat Rec* 189(3): 552; 1977. (no refs.)

78-0280 **Characteristics of Radiation-induced Pituitary-Thyroid Functional Disturbance in Relation to Pituitary and Thyroid Tumors in Rats (Meeting Abstract).**

(Eng) Lu, S. T. (Univ. Rochester, Rochester, NY). *Diss Abstr Int [B]* 38(6): 2563-B; 1977. (no refs.)

78-0281 **Highly Proliferative Monosomic Clones in the Bone Marrow of Irradiated Rats.** (Eng) Kohno, S. (Dept. Biology, Toho Univ., Funabashi, Japan); Ishihara, T. *Proc Jpn Acad* 53(2): 69-73; 1977.

Two monosomic clones derived from 2/7 Wistar rats who received a single x-ray dose of 700 R were characterized. The first clone, 70088-G, appeared after 4 mo and, by 9 mo, the frequency of monosomy was nearly 100%. The clone lacked one of the small metacentric chromosomes ranging from No. 14 to No. 18 and one unusually large marker in No. 2. The second clone, 73107-B, was noted at 3 mo and was prominent in all samples up to 14 mo. This clone was characterized by a loss of No. 17, a partial loss of the X chromosome, and a No. 1/No. 9 translocation. Further clonal evolution occurred in this case. Clone 73107-C appeared at 7 mo, and it was identical to 73107-B except for a duplication of the translocated No. 9 chromosome. Each monosomic clone was probably derived from its own original clone with radiation-induced abnormalities. Neither showed indications of neoplastic development. These monosomic clones may be radiation-induced chromosomal nondisjunctions that occurred several months after the radiation. (9 refs.)

78-0282 **The Induction of Chromosome Aberrations in Mouse Dictyate Oocytes by X-Rays and Chemical Mutagens.** (Eng) Caine, A. (MRC Radiobiology Unit, Harwell, Oxon, England); Lyons, M. F. *Mut Res* 45(3): 325-331; 1977.

Chromosome aberrations were induced in (C3H/HeH x 101/H)F<sub>1</sub> female mice after they were exposed to 400 rads' whole body x-irradiation or inoculated ip with 1.6 mg/kg triethylenemelamine (TEM) or 75 mg/kg isopropylmethanesulfonate (IPMS). After 1 wk, the percent maturation of control, TEM-, IPMS-, and x-ray-treated oocytes was 69%, 70%, 69%, and 59%, respectively; at 3 wk the respective figures were 73%, 79%, 73%, and 74%. With x-rays, aberrations were significantly higher after 3 wk than after 1 wk (59.5% vs 41.5%); with TEM and IPMS, there was a decrease in abnormal cells after 3 wk compared to 1 wk. The most common aberration with x-radiation was isochromatid fragments, but those with IPMS and TEM were chromatid gaps or breaks. (26 refs.)

78-0283 **Induction of Rectal Carcinoma in Mice by Local X-Irradiation.** (Eng) Hirose, F. (Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima 734, Japan); Fukazawa, K.; Watanabe, H.; Terada, Y.; Fujii, I.; Otsuka, S. *Gann* 68(5): 669-680; 1977.



The relationship between x-ray dose and induction of rectal carcinoma (RC) was determined by irradiating the pelvic region of random-bred female ICR-JCL mice and CF<sub>1</sub> mice with various doses at 1-wk intervals. Pneumonia was the most common cause of death in mice irradiated with small doses of x-rays, rectal and urethral obstructions in mice irradiated with large doses. Rectal obstruction consisted of ulceration, necrosis, or abscess formation in the rectal wall in the early stage and RC in the late stage. The incidence of RC in ICR mice was 0% after 1 dose of 2,000 rads, 31% after 1 dose of 3,000 rads, 6% after 2 doses of 1,500 rads, 25% after 3 doses of 1,500 rads, 42% after 2 doses of 2,000 rads, and 95% after 3 doses of 2,000 rads. The incidence was 70% in CF<sub>1</sub> mice exposed to two doses of 2,000 rads; in addition, 20% of these mice developed squamous cell carcinoma of the rectal mucosa. The x-ray induced RC's were tubular-, papillary-, and mucinous-type adenocarcinomas. They frequently showed invasive growth into the deep layers of the rectal wall. With invasion, the papillary type tended to change to the mucinous type. The incidence of RC increased and the latency time decreased with increase of divided as well as total dose of x-rays. RC's could not be observed in nonexposed control animals of both strains. (31 refs.)

**78-0284 Lymphocyte Cytotoxicity in X-Irradiation-induced Rat Small Bowel Adenocarcinoma. III. Blocking by 3 M KC1 Extract.** (Eng) Stevens, R. H. (Radiation Res. Lab., 14 Medical Labs., Dept. Radiology, Univ. Iowa, Iowa City, IA 52242); Brooks, G. P.; Osborne, J. W.; Hofmann, K. L.; Lawson, A. J. *J Immunol* 120(1): 335-339; 1978.

Factors associated with the x-radiation-induced Holtzman rat small bowel adenocarcinoma, which are capable of blocking in vitro lymphoid cell cytotoxicity, were identified in 3 M KCL extracts of the tumor tissue. Treatment of the KCL extracts with 50% saturated ammonium sulfate gave a soluble and an insoluble fraction, each of which contained elements that abrogated in vitro cytotoxic responses. The soluble fraction was more effective in blocking at the effector cell level, but the insoluble one operated at the target cell level. The oncofetal glycoprotein previously identified with the cellular membrane of this x-ray-induced malignancy was associated with both fractions. The insoluble fraction also contained immunoglobulins capable of binding to the tumor-associated oncofetal protein. The protective effects of the soluble fraction were citric acid-labile, a property previously reported for the oncofetal protein. Similar treatment of the insoluble fraction had no discernible effect on its ability to protect tumor cells from lymphoid cell destruction, but the oncofetal protein present in the extract no longer was immunologically detectable after acid treatment. The role of these blocking factors and the fetal antigen plus its immunoglobulins in the development and growth of x-ray-induced small bowel adenocarcinoma in rats must still be determined. (22 refs.)

**78-0285 Carcinoma of the Prostate in Irradiated Parabiotic Rats.** (Eng) Brown, C. E. (Cancer Res. Inst., New England Deaconess Hosp., Boston, MA 02215); Warren, S. *Cancer Res* 38(1): 159-162; 1978.

The carcinogenic effects of x-irradiation on the prostate were examined in 1,252 pairs of NEDH rats. Each pair was parabiosed; 60-90 days later, one partner received a single dose of 1,000 R x-radiation and the other rat was shielded with lead. Of the 1,120 pairs that survived >200 days, 25 irradiated partners developed malignant tumors of the prostate, 19 of which were adenocarcinomas. Two adenocarcinomas appeared in the shielded partners, and one appeared in a control group of 586 parabiosed and single rats. In all but five of the rats with prostatic cancer, primary tumors also occurred in other organs, the most common being pheochromocytomas of the adrenal gland, sarcomas at the anastomotic site, and islet cell adenomas of the pancreas. The x-irradiated rats were also subject to the effect of an altered hormonal milieu secondary to coincidental changes in the testes from irradiation. This, plus the association in some of the rats of endocrine tumors such as islet cell and adrenal medullary tumors, suggests the possibility of a contributing hormonal factor. It is concluded that the long-term effect of a single dose of 1,000 R whole-body x-radiation is weakly carcinogenic for the rat prostate. (16 refs.)

**78-0286 Cell Killing, DNA Repair, and Mutagenesis in Cultured Fibroblasts from Patients with Down Syndrome (Meeting Abstract).** (Eng) Yotti, L. (Michigan State Univ., East Lansing, MI); Glover, T. W.; Trosko, J. E.; Warren, S. T. *Am J Hum Genet* 29(6): 118A; 1977. (no refs.)

**78-0287 Changes in the Blood Composition of Rats after Combined Exposure to UV Rays and X-Rays** (Rus) Yatsula, G. S. (Dept. Nutrition and Hygiene, Kiev Inst. Advanced Training for Physicians, Kiev, USSR). *Gig. Sanit* (9): 95-97; 1977.

The effect of combined exposure to UV rays and x-rays on the hemopoietic system of albino female rats was studied. The animals received six x-irradiations at 7-day intervals (each dose ranged from 50 to 150 rads for total doses of 285, 570, 712, or 855 rads). Prior to this treatment, some of the rats had been subjected to prolonged (68 or 80 days) UV irradiation (10.25 mcal/cm<sup>2</sup>/2.5 min). The x-rays resulted in a dose-dependent decrease of WBC and an increase of RBC. However, these changes were less pronounced when rats were subjected to preirradiation with UV rays. (4 refs.)

**78-0288 A Fluence Response Study of Lethality and Mutagenicity of White, Black, and Blue Fluorescent Light, Sunlamp, and Sunlight Irradiation in Chinese Hamster Ovary Cells.** (Eng) Hsie, A. W. (Biology Div.



Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Li, A. P.; Machanoff, R. *Mutat Res* 45(3): 333-342; 1977.

Single-cell survival and mutation to 6-thioguanine resistance of Chinese hamster ovary CHO-K<sub>1</sub>-BH<sub>4</sub> cells were assayed to study their fluence response to white, black, and blue fluorescent light, a sunlamp, and sunlight. Exposure of cells to fluorescent white light at 550 Joules/m<sup>2</sup>/sec (JM<sup>2</sup>/s) resulted in a 35% reduction in survival after 120 min; an exposure time of 60-120 min was necessary for a significant increase in mutations. Fluorescent black light (2.9 J/m<sup>2</sup>/s) caused a 60%-70% reduction in survival within 120 min; mutation induction was increased after 60-120 min. Weak lethal and mutagenic effects were observed with fluorescent blue light (20 J/m<sup>2</sup>/s) after 60-120 min of treatment. When a plastic lid was placed between the fluorescent source and the cells, the biological effects of these light sources decreased. With exposure to a sunlamp at a distance of 91.44 cm, there was an exponential loss of cellular viability with increasing exposure time over 1.5 min; by 6 min, only 2% of the cells retained their reproductive capacity. A mutagenic effect was observed after 15 sec and it increased linearly up to 4.5 min. With exposure to sunlight, reproductive capacity was lost exponentially as a function of time for 12-60 min of exposure. Mutation induction increased linearly with time up to 30 min. The sunlight-induced 6-thioguanine-resistant variants possessed < 5% parental cellular hypoxanthine-guanine phosphoribosyl transferase activity, suggesting that mutation induction occurs at this locus. (36 refs.)

78-0289 **The Anatomical Distribution of Sunlight.** (Eng) Diffey, B. L. (Medical Physics Dept., Kent and Canterbury Hosp., Canterbury, Kent CT1 3NG, England); Perwin, M.; Davis, A. *Br J Dermatol* 97(4): 407-410; 1977.

The relative distribution of natural UV radiation to 10 sites on the surface of an unclothed manikin was measured using polysulfone film as the dosimeter. The measurements, made at Canterbury, England (latitude 51 N), on 19 days in late summer, indicated that vertical body surfaces received about one-half of the dose relative to the vertex. The relative doses at different sites were independent of weather conditions. (19 refs.)

78-0290 **Sister Chromatid Exchange in Babies Treated by Phototherapy (Letter to Editor).** (Eng) Gones-Villaescusa, V. J. (Section Genetics, Dept. Paediatrics, San Canalejo Hosp., La Coruna, Spain); Ugarte, M.; Izquez, A. *Lancet* 2(8047): 1084-1085; 1977.

The frequency of sister chromatid exchanges (SCE) was investigated in control and icteric babies and in full- and pre-icteric babies treated by phototherapy. The frequency of SCE per cell and per chromosome rose by 62% with respect to controls after 70 hr of phototherapy; distribution was directly related to chromosome length. After phototherapy,

SCE rose by 58% in four hyperbilirubinemic infants examined before and after treatment. It is suggested that G<sub>0</sub> lymphocytes may not be able to recover following radiation damage. (15 refs.)

78-0291 **Cancer Induction by Alpha-emitting Warm Particles (Meeting Abstract).** (Eng) Martell, E. A. (NCAR, CO). In: *Transactions of the American Nuclear Society. 1977 Winter Meeting. The San Francisco Hilton & Tower, Nov. 27-Dec. 2, 1977, San Francisco, CA.* Farmakes, R., ed. (La Grange Park, IL: American Nuclear Society): 125; 1977. (no refs.)

78-0292 **Tissue Changes Resulting from the Injection of  $\gamma$ -irradiated Cells into the Gynogenetic Teleost, *Poecilia formosa*.** (Eng) Woodhead, A. D. (Biology Dept., Brookhaven Natl. Lab., Upton, NY 11973); Setlow, R. B.; Hart, R. W. *Cancer Res* 37(12): 4261-4266; 1977.

After in vitro irradiation with  $\gamma$ -rays at 250 and 500 rads, *Poecilia formosa* cells were injected into young isogenic recipients, and 9 mo later the fish were examined grossly and histologically. Two of the most conspicuous changes were the development of extensive invasive thyroid hyperplasia and hypertrophy and the presence of large hemorrhages throughout the body, with reduction in the amount of hematopoietic tissue in the kidney and spleen. In a previous study, isogenic recipients of UV-irradiated *P. formosa* cells developed thyroid but not hematopoietic lesions. Possible reasons for this difference are discussed, including the nature of the DNA damage caused by UV and ionizing radiation, respectively. (10 refs.)

78-0293 **Is EPA's Radium-226 Drinking Water Standard Justified?** (Eng) Riddiough, C. R. (Sch. Public Health, Univ. Illinois Medical Center, Chicago, IL); Musselman, R.; Calabrese, E. J. *Med Hypotheses* 3(5): 171-173; 1977.

A proposal by the Environmental Protection Agency (EPA) to increase the permissible drinking water standard for <sup>226</sup>Ra from 3 to 5 picocuries/liter is reviewed, and four methodologies for estimating carcinogenic risk due to <sup>226</sup>Ra are compared. The EPA uses linear extrapolation models to estimate risks for low doses and low dose rates of high-LET (linear energy transfer) radiation; this approach may underestimate the risks. However, there is agreement between linear extrapolation models and epidemiological risk. Since those most at risk are the very young, because of their high mitosis rate and long life expectancy, it is not felt that the increase in <sup>226</sup>Ra exposure is justified on a human health basis. (17 refs.)



- 78-0294 Measurements of Endosteal Surface Areas in Human Long Bones: Relationship to Sites of Occurrence of Osteosarcoma.** (Eng) Spiers, F. W. (Univ. Leeds, Bone Dosimetry Res., Cookridge Hosp., Leeds, LS16 6QB, England); King, S. D.; Beddoe, A. H. *Br J Radiol* 50(599): 769-776; 1977.

The relationship between tumor appearance and endosteal area was studied to determine the relative potential of cortical and trabecular endosteum for tumor initiation. The femur, tibia, fibula, humerus, radius, and ulna of an adult human were studied, and the incidence of 33 radium-induced tumors and 612 naturally occurring tumors was determined in the proximal, middle, and distal sections of the bones. When tumor incidence for each section of bone was plotted against the trabecular surface area, tumor number was linearly related to this area. The correlation with cortical surface area, however, was poor. Furthermore, the number of tumors appearing in the middle third of the bone was less than that in the outer thirds. This result corresponded to the small fraction of trabecular area associated with the middle third. A study of the role of  $\alpha$ -particle dose in the radium-induced cancers indicated that its strongest influence on tumor incidence is in the area of trabecular surface at risk. However, area of surface at risk is a stronger factor than dose in influencing the site of tumor appearance. These findings support the hypothesis that tumor induction is proportional to the number of cells at risk. (12 refs.)

- 78-0295 An Estimate of Early Mortality and Morbidity Following Acute Inhalation of Plutonium.** (Eng) Goldman, M. (Univ. California at Davis, Davis, CA); Raabe, O. G. In: *Transactions of the American Nuclear Society, 1977 Winter Meeting. The San Francisco Hilton & Tower, Nov. 27-Dec. 2, 1977, San Francisco, CA.* Farmakes, R., ed. (La-Grange Park, IL: American Nuclear Society): 125-126; 1977.

A model for the effects of massive plutonium inhalation by man is presented based on findings in dogs. The LD50 for 1 yr is estimated to be 5,000 to 10,000 rads, with a central estimate of 6,700 rads. Morbidity from  $^{239}\text{Pu}$  during the first year could be expected with doses and burdens 5 to 10 times lower than acutely lethal doses. A 1-yr dose of 1,000 rads would be compatible with this estimate. (6 refs.)

- 78-0296 Thorotrast-induced Tumors Found in Autopsy Material.** (Ger) Hundsdorfer, S. (Pathologisches Institut der Medizinischen Akademie, DDR-301 Magdeburg, Leipziger Strasse 44, E. Germany); Bog, J.; Schultz, M. *Dtsch Gesundheitsw* 32(37): 1771-1775; 1977.

Postmortem examinations performed on 52,125 patients from 1957 to 1972 revealed 25 subjects with Thorotrast-induced tumors. Thorotrast had been used as a radiopaque

substance in x-ray exams in Magdeburg, E. Germany, from 1930 to 1946. There were 8 local tumors, 11 hepatocellular carcinomas, 4 intrahepatic cholangiomas, 2 hepatic hemangioma-endotheliomas, 1 squamous cell carcinoma of the kidney and 1 fibroplastic sarcoma of the elbow. The mean survival time after Thorotrast administration was 30 yr. Since tumor development is a function of dose and time, Thorotrast-related deaths can be expected to occur until about 1990. (49 refs.)

- 78-0297 Thymic Irradiation and Chronic Myelogenous Leukemia.** (Eng) Shimaoka, K. (Dept. Medicine B, Roswell Park Memorial Inst., State New York Dept. Health, Buffalo, NY); Sokal, J. E. *NY State J Med* 77(14): 2226-2230; 1977.

The case histories of two men, aged 26 and 25, who developed Philadelphia chromosome-positive chronic myelogenous leukemia 18 and 22 yr, respectively, after childhood thymic irradiation are presented. The total doses were 300 and 396 rads. The course of the disease typical. These patients probably represent examples of radiation-induced leukemia. (49 refs.)

- 78-0298 Radiation Cancers of the Pharynx and Esophagus. Report of Two Cases of Cancer of the Cervical Esophagus.** (Fre) Charles, J. (Louvain, France); Fiasse, R.; Pringot, J.; Longueville, J.; Wambersie, A.; Haot, J.; Dive, C. *Rev Fr Gastroenterol* (132): 65-66; 1977.

Radiation-induced cancer of the esophagus occurred in two women 21 and 50 yr after low-voltage radiation therapy for goiter. The dose responsible was thought to be about 2,500 rads. (no refs.)

*See also:*

- \* (Rev.): 78-0009, 78-0010, 78-0011, 78-0012, 78-0013, 78-0022, 78-0068, 78-0069, 78-0070, 78-0071, 78-0072, 78-0082, 78-0108, 78-0109.  
 \* (Chem.): 78-0125, 78-0151, 78-0156, 78-0222, 78-0255.  
 \* (Immun.): 78-0429, 78-0434.  
 \* (Path.): 78-0470, 78-0492, 78-0494, 78-0500, 78-0507, 78-0509, 78-0534, 78-0535.  
 \* (Epid.-Biom.): 78-0569, 78-0570.



## VIRAL CARCINOGENESIS

**78-0299 Cell-Free Synthesis of the Precursor Polypeptide for Avian Myeloblastosis Virus DNA Polymerase.** (Eng) Paterson, B. M. (Lab. Biochemistry, NCI, NIH, Bethesda, MD 20014); Marciani, D. J.; Papas, T. S. *Proc Natl Acad Sci USA* 74(11): 4951-4954; 1977.

The 35S RNA isolated from avian myeloblastosis virus (AMV)-infected chicks directed the cell-free synthesis of two polypeptides of mol wt 180,000 and 76,000 daltons. The latter has previously been identified as a precursor to the *gag* structural proteins; the former was not synthesized in response to AMV RNA sedimenting at  $\leq 30S$ . The 180,000-dalton protein can account for all peptides of AMV DNA polymerase and those of the *gag* viral proteins. Furthermore, 19/22 peptides characteristic of the 76,000-mol wt polypeptide were accounted for in the tryptic pattern of the 180,000-dalton polypeptide. These results indicate that the *gag* and polymerase genes are adjacent on the avian oncornavirus genome, because the two can be translated as a single polypeptide in a cell-free system. Thus, the structural order of avian reoviruses is 5'-*gagpol-env-srd(leuk)*-poly(A)-3'. A model for the in vivo processing of the viral polymerase is proposed. (22 refs.)

**78-0300 Revertase in Myeloblasts of Chickens Infected with Avian Myeloblastosis Virus.** (Pol) Bartnikowa, W. (Lab. Clinical Analysis and Biochemistry, Inst. Oncology, Gliwice Div., ul. Armii Czerwonej 15, 44-101 Gliwice, Poland). *Acta Haematol Pol* 8(3): 189-195; 1977.

Reverse transcriptase isolated from the myeloblasts of chickens infected with avian myeloblastosis virus failed to synthesize viral DNA in vitro using the endogenous virus as template. The failure was traced to a lack of completely formed viral RNA in the immature virus particles. (23 refs.)

**78-0301 Virological and Immunological Characteristics of Tumors Induced in Adult Rats by Rous Sarcoma.** (Eng) Shevlyaghin, V. Ya. (Gamaleya Inst. Epidemiology and Microbiology, Moscow, USSR); Kusnetzova, N. N.; Biryulina, T. I. *Neoplasma* 24(5): 521-527; 1977.

Forty primary tumors induced by the Schmidt-Ruppin strain of Rous sarcoma virus (RSV) in Wistar rats and the first seven tumor passages in August rats were examined. The tumors were divided into four groups on the basis of virus-cell interactions. The first group (2/40 Wistar) contained mature forms of RSV with latent period of 15 and 20 days. Viral

antigens were found in 35% and 68% of the tumor cells, and the sera contained virus-neutralizing antibodies. Group-specific (gs) antigen and its antibodies were not detected. The second group, composed of 19 Wistar rat tumors (latent period 1-5 mo) and the first seven passages in August rats, contained RSV connected with the cells. Cell-free tumor extracts did not produce sarcomas in chicks, and virus-neutralizing antibodies were absent from the rat sera. Irradiation of the tumor cells with 5,000 to 10,000 R did not rescue the virus. Viral antigens were detected in 8/9 tumors in 26% to 42% of the cells. Gs antigen was discovered in 1/16 tumors and its antibodies in 17/19 sera samples. In five cases, the presence of viral antigen coincided with the detection of gs antibodies in the sera. The first passages of August tumors were virogenic. Viral and gs antigens were detected after these passages, but decreased in subsequent passages. The sera did not contain virus-neutralizing and complement-fixing gs antibodies. The third group was composed of virus-free Wistar rat tumors (8/40) with a latent period of 15-30 days. Cell association activated the virus, but irradiation (5,000 to 10,000 R) had no effect. Viral antigens were found in two tumors in 28% and 38% of the cells, respectively. Gs antigen was discovered in 4/5 tumors, and antibodies to the antigen were discovered in 3/8 sera; virus-neutralizing antibodies were not found. In the fourth group, the Wistar rat tumors (11/40) were virus-free and did not respond to activation of RSV. Gs antigen was found in one tumor; viral antigens, virus-neutralizing antibodies, and complement-fixing antibodies were not detected. (15 refs.)

**78-0302 Cell Membrane Structure and Cell Surface Tumor Antigens of Rous Sarcoma Virus (RSV)-transformed BHK Fibroblasts.** (Ita) Comoglio, P. M. (Istituto di Anatomia Umana Normale, Università di Torino, Turin, Italy); Tarone, G.; Bertini, M.; Prat, M. *Minerva Med* 68(51): 3533-3534; 1977.

This study of Rous sarcoma virus-transformed hamster kidney fibroblasts (B4 cells) suggests that differences in the membrane structures of B4 and normal C13 cells are due to an altered conformational disposition of identical or similar proteins in the biomolecular lipid layer. (7 refs.)

**78-0303 Unilateral Phenotypic Mixing of Envelope Antigens Between Togaviruses and Vesicular Stomatitis Virus or Avian RNA Tumour Virus.** (Eng) Zavadova, Z. (Inst. Virology, Slovak Acad. Sciences, Bratis-



lava, Czechoslovakia); Zavada, J.; Weiss, R. *J Gen Virol* 37(3): 557-567; 1977.

The possibility of phenotypic mixing between the togaviruses Sindbis virus (SbV), belonging to the alphavirus group, and Langat virus, belonging to the flavivirus group, with vesicular stomatitis virus (VSV) was investigated. When heat stabilization of the thermolabile TIB17 mutant of VSV was neutralized by the corresponding antisera, no SbV(VSV) pseudotypes were observed. Avian RNA tumor virus (ATV) in mixing infection with SvV produced a proportion of phenotypically mixed particles containing ATV genomes and SbV antigens, but no detectable particles containing SbV genomes and ATV envelope antigens. SbV acted as a helper virus for envelope-defective Rous sarcoma virus (RSV). When a avian helper virus was also present in mixed infection, more than 90% of the RSV particles bearing SbV envelope antigens also bore ATV antigens and were doubly neutralizable by antisera specific to either parent virus. When experiments were performed with Langat virus and VSV, some doubly neutralizable particles containing VSV genomes were produced; however, no pure pseudotypes were detected. Thus VSV and RSV readily mixed phenotypically with other enveloped viruses to the group of togaviruses. SbV may have a more specific requirement for the assembly of related togavirus envelope glycoproteins than have VSV and oncoviruses, which exhibit less stringent recognition. (24 refs.)

**78-0304 General Immunocompetence of Rats Bearing Avian Sarcoma Virus-induced Intracranial Tumors.** (Eng) Roszman, T. L. (Div. Experimental Pathology, Dept. Pathology, Coll. Medicine, Univ. Kentucky, Lexington, KY 40506); Brooks, W. H.; Markesbery, W. R.; Bigner, D. D. *Cancer Res* 38(1): 74-77; 1978.

The mitogenic responsiveness of spleen cells obtained from Fischer 344 rats inoculated intracranially with avian sarcoma virus (ASV) was studied. Sixty percent of the rats had astrocytomas, 3 sarcomas, 7% mixed gliosarcomas, and 20% showed no evidence of tumors. Spleen cells from rats bearing astrocytomas had a significantly reduced response to phytohemagglutinin (PHA: 10 and 20  $\mu$ g) and concanavalin A (Con A: 0.01 - 50  $\mu$ g) compared to the response of normal controls. The response of spleen cells from virus-inoculated rats not bearing tumors and from rats with sarcomas did not differ from control responses at any concentration of PHA or Con A. The rats with the largest astrocytomas had significantly lower responses to concentrations of PHA or Con A. The rats with the largest astrocytomas had significantly lower responses to concentrations of PHA from 5 to 50  $\mu$ g than those of controls. Rats with small or medium astrocytomas did not have significantly impaired responses to PHA. Decreased Con A responses were observed regardless of tumor size; spleen cells from rats bearing the larger astrocytomas were most affected. These results indicate that the ASV-induced astrocytoma in rats is an immunological parallel of

the human disease, based on the loss of general immunological competence as assessed by the responsiveness of lymphocytes to PHA and Con A. (20 refs.)

**78-0305 Structural Protein Markers in the Avian Oncoviruses.** (Eng) Rettenmier, C. W. (Rockefeller Univ., New York, NY 10021); Hanafusa, H. *J Virol* 24(3): 850-864; 1977.

Electrophoresis in high-resolution polyacrylamide gels was used to analyze the structural proteins of avian leukosis-sarcoma viruses (ALSV). The p19 proteins of Rous-associated virus (RAV)-2, RAV-1, and the Bryan high-titer strain of Rous sarcoma viruses had higher electrophoretic mobilities than the p19's of other viruses. The p27 protein of RAV-O and the p15 protein of RAV-7 had lower electrophoretic mobilities than the corresponding proteins of other ALSV. The altered mobility of the p19 proteins was correlated with specific differences in the tryptic peptides of these proteins; this finding did not hold for the p27 and p15 proteins. Viral protein markers were used to study the structural proteins of subgroup E RAV-60 produced after infection of chicken embryo cells with exogenous ALSV. Although exogenous group-specific protein markers were frequently detected in the subgroup E isolates, one RAV-60 had a p27 that comigrated with the p27 of RAV-O. The p19s from either RAV-O or the exogenous viruses. These findings suggest that RAV-60 is generated by recombination between endogenous and exogenous oncoviruses (presumably from crossing-over at the gag genes), and they indicate that the p27 encoded by RAV-O is closely related to a protein specified by endogenous viral information in chicken cells. Thus, electrophoretic variants can be used as unselected markers in genetic studies of RNA tumor viruses. (52 refs.)

**78-0306 Turnover of Cellular Carbohydrates in Normal and Rous Sarcoma Virus-transformed Cells.** (Eng) Leonard, J. G. (Dept. Biochemistry, Univ. Illinois, Urbana, IL 61801); Hale, A. H.; Roll, D. E.; Conrad, H. E.; Weber, M. J. *Cancer Res* 38(1): 185-188; 1978.

The possible role of nonspecific degradation of carbohydrates containing polymers in generating differences between normal and transformed cell surfaces was examined in chicken embryo fibroblasts infected with a temperature-sensitive (ts) mutant of Rous sarcoma virus, RSV-T5<sup>6</sup>. The distribution of glucosamine-labeled polymers was analyzed on the cell surface, in the growth medium, and in the cell cortex, and the net turnover of these polymers was determined in normal cells and in cells in the process of malignant transformation. The distribution of label and the turnover kinetics for hyaluronic acid, total glycoproteins, and chondroitins were identical in normal and transforming cultures. It is concluded that large-scale nonspecific hydrolysis of cell-surface carbohy



rate polymers is unlikely to be responsible for generating or maintaining the differences in surface composition seen between normal and transformed cells. (17 refs.)

- 8-0307 **Plasma Membrane Proteins Exposed on the Outer Surface of Control and Rous Sarcoma Virus-transformed Hamster Fibroblasts.** (Eng) Tarone, G. (Dept. Human Anatomy, Univ. Torino, Sch. Medicine, 0126 Torino, Italy); Comoglio, P. M. *Exp Cell Res* 110(1): 143-152; 1977.

The protein composition of the plasma membrane of C13 baby hamster kidney (BHK) fibroblast cells and Rous sarcoma virus (RSV)-transformed B4 BHK cells was investigated. On electrophoresis, the C13 cells showed seven major peaks, A, B, C, D, E, F, and S, with approx mol wts of 50,000 (150K)-200K, 90K-110K, 70K-75K, 44K-40K, 30K-45K, 30K-40K, and < 23K daltons, respectively. Electrophoresis of the B4 membrane proteins revealed a similar pattern, but coelectrophoresis indicated that one peak, C', of B4 cells had a 4% difference in relative mobility and an approx difference in mol wt of 5K-10K daltons. Additional experiments were performed with the 14B line of BHK fibroblasts transformed by the FU19 temperature-sensitive mutant RSV. The electrophoretic pattern of these cells showed the same displacement of C to C' when the cells were grown at 37 C but a pattern similar to that of C13 cells when they were grown at 41 C. Further chromatographic analysis indicated that the displacement of peak C was due to the presence of an extra component not detectable in the peak C of C13 cells. It is concluded that the gene coding for this protein is intimately associated with transformation. (48 refs.)

- 8-0308 **Intracellular Cleavage of Rous Sarcoma Virus Protein Precursor after Fusion-Injection of Purified Viral Protein p15 into Non-Permissive Hamster Cells (Meeting Abstract).** (Eng) von der Helm, K. (Swiss Inst. Experimental Cancer Res., Ch. des Boveresses, CH-1066 Epalinges s/Lausanne, Switzerland); Wille, W.; Wilke, K. *Hoppe Seylers Z Physiol Chem* 358(10): 1216-1217; 1977. (2 refs.)

- 8-0309 **Extensive Reverse Transcription of RSV Genome by Nucleic Acid-binding Protein.** (Eng) S. G. (Molecular Virology Lab., Abbott Labs., North Chicago, IL 60064); Hung, P. P. *Nature* 270(5635): 366-369; 1977.

The effect of a 30,000-mol wt DNA-binding protein isolated from chicken fibroblasts on reverse transcriptase activity in Rous sarcoma virus (RSV) in a reconstituted system was investigated. Binding of the protein on synthetic polynucleotides increased linearly until the protein saturated the

binding capacity. Significant decreases were observed in protein binding to synthetic polynucleotides when NaCl concentrations reached 0.05 M or higher. However, the binding of 70S labeled RSV RNA by the protein decreased only 10% with 0.2 M NaCl. Evidence obtained from UV hyperchromicity studies indicated that RSV RNA unwound rapidly after contact with the binding protein. The hyperchromic effect was reversible on addition of NaCl, suggesting that the RNA had been deproteinated and returned to the folded structure. Various preparations of the binding protein added to a reconstituted system slowed the gel mobility of the DNA products due to the formation of large products. If the binding protein solution was heated to 65 C for 10 min before addition to the system, the large products were not formed and mobility was unaffected. Ninety-five percent of the DNA product annealed to the RSV RNA and was resistant to endonuclease digestion. Thus, the RSV reverse transcriptase was able to synthesize an almost complete DNA copy from purified viral RNA in the presence of the binding protein. (27 refs.)

- 78-0310 **A Joint Product of the Genes gag and pol of Avian Sarcoma Virus: A Possible Precursor of Reverse Transcriptase.** (Eng) Oppermann, H. (Dept. Microbiology, Univ. California, San Francisco, CA 94143); Bishop, J. M.; Varmus, H. E.; Levintow, L. *Cell* 12(4): 993-1005; 1977.

A virus-specific protein of approximately 180,000 daltons was identified in chicken embryo fibroblasts transformed by avian sarcoma virus (ASV). ASV-transformed cells were labeled with <sup>35</sup>S-methionine, and cytoplasmic extracts were prepared and treated with different antisera directed against various viral structural proteins. The polypeptides precipitated by the various antisera were analyzed by gel electrophoresis. The proteins that were precipitated from transformed cells with antiserum against p27, the major viral core protein, included p27 and at least five proteins of higher mol wt. The most prominent of these was Pr76 gag, which has been identified as the common precursor from which the core proteins are derived. A slowly migrating protein with an electrophoretic mobility comparable to a mol wt of 180,000 daltons (P180) was also precipitated by anti-p27. Antiserum directed against purified reverse transcriptase also recognized a protein with electrophoretic mobility identical to that of P180 in transformed cells. In accord with previous reports, studies of the competitive inhibition of immunoprecipitation of P180 indicated that Pr76 gag carried the immunological determinants of p27 and, presumably, the other proteins of the viral core. P180 carries similar determinants in addition to those specific for reverse transcriptase. The tryptic peptides of P180 represent the sum of those of the precursor of the core proteins (Pr76 gag) and reverse transcriptase, indicating that P180 must arise from the uninterrupted translation of gag and pol. The kinetics of its formation and decay suggest that P180 is the precursor of reverse transcriptase. (24 refs.)



**78-0311 Genetic Control of Response to Rous Sarcoma Viruses in Rhode Island Red Fowl (Meeting Abstract).** (Eng) Dren, C. (Veterinary Res. Inst. Hungarian Acad. Sciences, Budapest, Hungary); Pani, P. K.; Payne, L. N. *Acta Microbiol Acad Sci Hung* 24(1): 76; 1977. (no refs.)

**78-0312 Genetic Control of Rous Sarcoma Regression in Chickens: Linkage with the Major Histocompatibility Complex.** (Eng) Schierman, L. W. (Dept. Pathology, New York Medical Coll., Valhalla, NY 10595); Watanabe, D. H.; McBride, R. A. *Immunogenetics* 5(4): 325-332; 1977.

Two closely related inbred chicken strains, G-B1 (genotype B<sup>1</sup>/B<sup>1</sup>) and G-B2 (genotype B<sup>1</sup>/B<sup>2</sup>), and the F<sub>1</sub> offspring from a cross between G-B1 and G-B2 birds were inoculated with Rous sarcoma virus (RSV; 3,600 focus-forming units). All G-B1 birds developed progressively growing tumors that resulted in their death, but most G-B2 and F<sub>1</sub> birds developed small tumors that subsequently regressed. The results with F<sub>1</sub> birds suggest that the ability to regress Rous sarcomas is a dominantly inherited trait. Progeny from a backcross mating were also challenged with RSV to determine whether the development of RSV-induced tumors is controlled by genes at a single locus in these lines. The results demonstrated that Rous sarcoma regression was associated with the B genotype. Evidence for crossing over between the genes controlling serologically determined major histocompatibility complex (MHC) antigens on RBC and genes controlling Rous sarcoma growth was also obtained. The MHC-linked gene that confers the ability to regress Rous sarcomas was designated R-Rs-1. The allelic gene that allows for progressive tumor growth in homozygous birds was designated r-Rs-1. It is concluded that regression of RSV-induced tumors is a dominantly inherited trait, controlled by a gene within or closely linked to the MHC (B region). (19 refs.)

**78-0313 Evidence for Complementary Action of *tvb* and *ve* Genes that Control Susceptibility to Subgroup E RNA Tumour Virus in Chickens.** (Eng) Pani, P. K. (Houghton Poultry Res. Station, Houghton, Huntingdon, Cambs PE17 2DA, England). *J Gen Virol* 37(3): 639-446; 1977.

The susceptibility of the inbred chicken lines 7-2, E and Reaseheath C to challenge by Rous sarcoma virus (RAV 2) of subgroup B and Rous sarcoma virus (RAV o) of subgroup E, was investigated. The E line carried the *es* gene and lacked the inhibitor (*Ic*) gene. Reaseheath C had a *bsbs* genotype. Line 7-2 lacks the *Ic* gene but carries the *brbrer* genotype. All embryos of line E are susceptible to subgroup B virus and approx 80% are susceptible to subgroup E. All 7-2 embryos are resistant to both subgroup E and subgroup B viruses. Av E-virus susceptibility of the E line could be increased or de-

creased by addition or subtraction, respectively, of the *bs* gene. These findings fit the two-gene model with complementary gene action and are inconsistent with the single-gene model of multiple allelism of the *tvb* locus. (17 refs.)

**78-0314 Subgenomic, Cellular Rous Sarcoma Virus RNAs Contain Oligonucleotides from the 3' Half and the 5' Terminus of Virion RNA.** (Eng) Mellon, P. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, CA 94720); Duesberg, P. H. *Nature* 270(5638): 631-634; 1977.

Polyadenosine(A)-tagged Rous sarcoma virus specific RNAs synthesized during a 3 hr <sup>32</sup>P labeling period in infected cells were isolated and characterized. Hybridization experiments indicated that the infected cells contain viral RNA species that consisted of a capped segment from the 5' end of virion RNA attached to a polyadenylated longer segment from the 3' end. These findings suggest that subgenomic Rous sarcoma virus RNAs are synthesized by a splicing mechanism analogous to that observed in adenovirus or by transcription from specifically deleted proviral DNAs. The data do not support the suggestion that subgenomic RNAs are generated by cleavage of 35 to 40S RNA or by internal transcription of full-length provirus. (24 refs.)

**78-0315 Cell-free Translation of Avian Oncornavirus RNA (Meeting Abstract).** (Eng) Purchio, A. F. (Univ. Colorado, Boulder, CO). *Diss Abstr Int [B]* 38(5): 2127B-2128B; 1977. (no refs.)

**78-0316 Transformation in Vitro of Glial Hamster Cells by Rous Sarcoma Virus.** (Eng) Rabotti, G. F. (Laboratoire de Medecine Experimentale, College de France, 75231 Paris Cedex 05, France); Gogusev, J.; Teutsch, B.; Mongiat-Lardemer, F.; Haguenau, F. *J Natl Cancer Inst* 60(1): 113-124; 1978.

The ability of the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV-2) to infect normal glial cell lines from inbred CF hamster embryos cultivated in vitro was investigated. These cells contained the nervous system-specific protein S-100 throughout their cytoplasm, but mostly in the perinuclear region. Foci of transformation were noted 3 to 4 wk after RSV infection. Electron microscopic features of the normal and transformed cells with different morphologies are listed. Cocultivation of the transformed cells with chick embryo fibroblasts of phenotype C/E resulted in rescue of the virus. The rescued virus was neutralized by chicken antiserum specific for subgroup B virus, and antiserum against SR-RSV-2 was again capable of neutralizing all subgroup B viruses. Antiserum against subgroup A virus was ineffective.



Inoculation of young CF hamsters with  $5 \times 10^4$  cells resulted in 100% tumor development within 1 mo. Histologically, these tumors were gliomas. (26 refs.)

**78-0317 Transformation-defective Mutants of Rous Sarcoma Virus with *src* Gene Deletions of Varying Length.** (Eng) Kawai, S. (Dept. Oncology, Inst. Medical Science, Univ. Tokyo, Japan); Duesberg, P. H.; Hanafusa, H. *J Virol* 24(3): 910-914; 1977.

Transformation-defective (*td*) mutants of the Schmidt-Ruppin strain of Rous sarcoma virus (RSV), subgroup A, which were judged to contain deletions in the sarcoma (*src*) gene, had RNA's that varied in size when compared by electrophoresis. Three of seven *td* mutants recombined with a Schmidt-Ruppin mutant of RSV that has a temperature-sensitive *src* gene (*ts68*) to give rise to recombinants with a reduced temperature sensitivity. None of these recombinants had properties identical to wild-type virus. These results suggest that some *td* clones have total deletions in the *src* gene, but others have only partial deletions. There was no direct correlation between RNA size and extent of *src* gene deletion. (21 refs.)

**78-0318 Recovery of Avian Sarcoma Virus from Tumors Induced by Transformation-defective Mutants.** (Eng) Hanafusa, H. (Rockefeller Univ., New York, NY 10021); Halpern, C. C.; Buchhagen, D. L.; Kawai, S. *J Exp Med* 146(6): 1735-1747; 1977.

Transformation-defective (*td*) mutants of the Schmidt-Ruppin strain of Rous sarcoma virus (RSV), which contains deletions in the gene responsible for transformation (*src* gene), were unable to transform chicken embryo fibroblasts *in vitro*. Injection of some of the *td* mutants into newborn chickens resulted in the formation of sarcomas from which sarcoma virus was consistently recovered. The possibility that transforming RSV was present in the *td* virus preparations was excluded by further purification of the *td* viruses. The morphology of the foci induced by the newly recovered sarcoma virus was distinct from that of foci induced by the parental Schmidt-Ruppin strain of RSV. It is suggested that the new sarcoma virus was generated as a result of the genetic interaction between the genomes of *ts* virus and chicken cells. (45 refs.)

**78-0319 Quantitative Determination of Myoinositol, Inositol 1-Phosphate, Inositol Cyclic 1:2-Phosphate and Glycerolphosphoinositol in Normal and Rous-Sarcoma-Virus-transformed Quail Fibroblasts under Different Growth Conditions.** (Eng) Diring, H. (Robert-Koch-Institut des Bundesgesundheitsamtes, Nordufer 20, D-1000 Berlin 65, W. Germany); Koch-Kallnbach, M. E.; Friis, R. R. *Eur J Biochem* 81(3): 551-555; 1977.

The presence of myoinositol and its phosphorylated derivatives was determined in normal Japanese quail embryo cells and in those transformed by Prague strain Rous sarcoma virus, subgroup A. Exponentially growing normal and tumor cells contained 25-40 nanomoles (nmol) free inositol, 0.40-0.45 nmol myoinositol 1-phosphate, 0.30-0.50 nmol glycerolphosphoinositol (GPI), and 0.03-0.04 nmol myoinositol cyclic 1:2-phosphate, per  $\mu$ mol phospholipid. At high cell populations in the absence of serum (conditions halting normal but not tumor cell growth), the levels of GPI and free inositol increased to 0.64 and 64 nmol, respectively. In normal cells, GPI increased to 0.95 nmol and free inositol increased to 144 nmol. With short pulses of  $^3\text{H}$ -myoinositol, the specific activities of inositol 1-phosphate and inositol cyclic 1:2-phosphate were highest after 1-8 hr, regardless of cell type or growth conditions. The specific activities of phosphatidylinositol and GPI increased more slowly. (24 refs.)

**78-0320 Failure of Cultured Chick Embryo Fibroblasts to Incorporate Collagen into Their Extracellular Matrix When Transformed by Rous Sarcoma Virus: An Effect of Transformation but Not of Virus Production.** (Eng) Arbogast, B. W. (Specialized Center for Thrombosis Res., Temple Univ. Sch. Medicine, 3400 N. Broad St., Philadelphia, PA 19140); Yoshimura, M.; Kaji, A.; Kefalides, N. A.; Holtzer, H. *J Biol Chem* 252(24): 8863-8868; 1977.

Collagen synthesis was examined in cultured chick embryo fibroblasts (CEF) infected with Prague wild-type Rous sarcoma virus (RSV) and with a temperature-sensitive (*ts*) mutant of this strain, RSVtsLA24. Normal CEF and CEF infected with the *ts* mutant and cultured at the nonpermissive temperature secreted procollagen into the medium and incorporated collagen into their extracellular matrix. This was shown by carboxymethyl (CM)-cellulose and sodium dodecyl sulfate-polyacrylamide disk gel (SDS) electrophoresis. Transformed CEF and CEF infected with the *ts* mutant and cultured at the permissive temperature secreted procollagen into the medium, but there appeared to be no conversion of procollagen into collagen nor incorporation of collagen into the extracellular matrix. No radioactive collagen peaks were apparent upon CM-cellulose or SDS-polyacrylamide disk gel electrophoresis. The observation that cells infected with the *ts* mutant incorporate collagen into their extracellular matrix at the nonpermissive temperature demonstrates that virus production does not interfere with collagen processing. The block in procollagen processing seen in the infected cells at the permissive temperature is, therefore, a result of transformation alone. (36 refs.)

**78-0321 Proventriculitis, "Nakanuke" and Reticuloendotheliosis in Chickens Following Vaccination with Herpesvirus of Turkeys (HVT).** (Eng) Jackson, C. A. (New South Wales Dept. Agriculture, Veterinary Res. Station, Glenfield, New South Wales, 2167, Australia); Dunn,



S. E.; Smith, D. I.; Gilchrist, P. T.; MacQueen, P. A. *Aust Vet J* 53(9): 457-459; 1977.

Laboratory data on studies of 38 chickens with reticuloendotheliosis proventriculitis, nakanuke (adhesions of barbs to central portion of feather shaft) and nervous system disorders as a result of vaccination with herpesvirus of turkeys are presented. At the same time, it was discovered that an attenuated Marek's disease virus vaccine produced similar lesions in chickens. Both vaccines had been produced on an avian cell substrate from the same source, and the transmissible agent was thought to be reticuloendotheliosis virus. (4 refs.)

**78-0322 Primary Tumours Induced by MC29 Virus in Turkeys (Meeting Abstract).** (Eng) Schaff, Z. (First Inst. Pathology, Semmelweis Univ. Medical Sch., Budapest, Hungary); Talas, M.; Stoger, I.; Foldes, I.; Lapis, K. *Acta Microbiol Acad Sci Hung* 24(1): 75; 1977. (no refs.)

**78-0323 Structure and Function of Virus-induced Antigens in Cultured Cells Infected with Marek's Disease and Turkey Herpes Viruses. II. Isolation of Intracellular Antigen from Infected Cells.** (Ger) Kaaden, O. R. (Bundesforschungsanstalt für Viruskrankheiten der Tiere, Paul-Ehrlich-Str. 28, D-7400 Tübingen, W. Germany). *Med Microbiol Immunol (Berl)* 163(3): 157-181; 1977.

Virus-induced antigens isolated from cell cultures infected with Marek's disease (MDV) and turkey herpes viruses (HVT) were characterized. The antigens were isolated by salt extraction and purified by chromatography and isoelectric focusing. Electrophoretic analysis of  $^{35}\text{S}$ ,  $^3\text{H}$  and  $^{32}\text{P}$  labeled antigens revealed seven different polypeptides, two of them containing labeled carbohydrates and one phospholipid component. Serologically, the antigens were active membrane complexes carrying common antigenic determinants of MDV and HVT; virus neutralizing immunoglobulins bound to them. It is suggested that MDV and HVT be classified as different serotypes of a common Marek's disease virus group. (69 refs.)

**78-0324 Structure and Function of Virus-induced Antigens in Cultured Cells Infected with Marek's Disease and Turkey Herpes Viruses. I. Alteration of the Immunological Specificity of Plasma Membranes in Infected Cells.** (Ger) Kaaden, O. R. (Bundesforschungsanstalt für Viruskrankheiten der Tiere, Paul-Ehrlich-Str. 28, D-7400 Tübingen, W. Germany). *Med Microbiol Immunol (Berl)* 163(3): 141-156; 1977.

Virally induced proteins were observed in the plasma membranes of cultured cells infected with both Marek's disease

(MDV) and turkey herpes viruses (HVT) and characterized. The membrane proteins induced virus-neutralizing antibodies which protected inoculated chickens against challenge with oncogenic MDV. Electrophoresis demonstrated at least two other virus-induced proteins in the plasma membranes of infected cells: the solubilized membrane proteins formed two precipitin lines when reacted with MDV antisera. Hyperimmune sera against the membrane antigens neutralized infectious cell-free HVT. The buoyant density of the plasma membranes was found to be increased by 30 mg/ml to 1.08 g/ml. Although vaccination of chickens with purified plasma membrane preparations from HVT-infected cells reduced mortality and lesions by 94%, analogous membrane alterations were never observed in the membranes of Marek's disease lymphoblastoid tumor cells. (69 refs.)

**78-0325 Abelson Virus-Transformed Lymphocytes: Null Cells that Modulate H-2.** (Eng) Pratt, D. M. (Div. Basic Sciences, Sidney Farber Cancer Inst., Boston, MA 02115); Strominger, J.; Parkman, R.; Kaplan, D.; Schwaber, J.; Rosenberg, N.; Scher, C. D. *Cell* 12(3): 683-690; 1977.

Abelson murine leukemia virus (A-MuLV)-transformed lymphoid cells from BALB/c mice were characterized as null lymphocytes. Study of five in vitro-transformed lines failed to reveal  $\theta$ -antigen on the cell membranes, in contrast to the Moloney MuLV (M-MuLV)-induced thymic cell lines. Neither M-MuLV nor A-MuLV had detectable surface immunoglobulin (Ig), but one A-MuLV-transformed cell line (BM18-8) synthesized a cell-associated polypeptide that comigrated with the  $\mu$  heavy chain. Two Ig myelomas, MPC 11 and MOPC 104E, produced at least 100 times more heavy chain per cell than BM18-8. Fc receptors were present in A-MuLV-transformed cells, and they expressed H-2D and H-2K but not H-2I histocompatibility antigens; the H-2D antigen was lost with passage in vitro. Injection of A-MuLV cell lines into (BALB/c x C57BL/6) $F_1$  mice resulted in tumors in most mice. The tumor cells contained more H-2D than cells passaged in vitro. Cloning of BM18-8 cells (5% to 30% lysed by anti-H-2D) resulted in 11 clones that could also be lysed to varying degrees (13% to 69%); thus A-MuLV-transformed cells must modulate H-2D in vitro. Incubation of BM18-8-15 cells (approx 15% lysable) with anti-H-2D sera before injection in vivo indicated that A-MuLV-transformed cells modulate H-2 to higher levels in vivo and to lower levels in vitro; these higher levels were not due to selective growth of a subpopulation with high H-2 levels. (26 refs.)

**78-0326 Cellular and Viral Factors in the Tumorigenesis and Immunogenesis in Actinomycin-D Sensitive and Resistant L1210(V)gin- Leukemia Cells (Meeting Abstract).** (Eng) Calvelli, T. A. (Cornell Univ. Medical Coll., Ithaca, NY). *Diss Abstr Int [B]* 38(5): 1996B-1997B; 1977. (no refs.)



78-0327 **Study of the Oncogenic Potential of Cultured Human Skin Fibroblasts Derived from Individuals with Hereditary Adenomatosis of the Colon and Rectum: The Biochemical Events Associated with Infection and Transformation by Kirsten Murine Sarcoma Virus (Meeting Abstract).** (Eng) Pinphanichakarn, P. (Univ. Texas, Austin, TX). *Diss Abstr Int [B]* 38(5): 2162B; 1977. (no refs.)

78-0328 **An Electron Microscopic Study of Hepatic Erythropoiesis in Adult Mice with Friend Virus Disease.** (Eng) Orlic, D. (Dept. Anatomy, New York Medical Coll., Basic Science Building, Valhalla, NY 10595); Miand, E. A. *Lab Invest* 37(6): 579-587; 1977.

Microscopic analyses of adult female DBA/2 mouse liver were performed 2 to 14 days after injection of  $7.3 \times 10^3$  spleen focus-forming units of a polycythemia-inducing strain of Friend virus. Erythroblasts were evident in the lumina of sinusoids as early as 2 days after inoculation. These foci increased through day 14 when they were observed throughout the liver. There was virtually no evidence of hepatic myelopoiesis; but megakaryoblasts were present in increasing numbers on days 9 through 14. However, platelet release was never observed. Extensive ineffective erythropoiesis involving erythroblast death occurred within the proliferative foci. Death may have been related to large inclusions in the cytoplasm of erythroblasts that were thought to be autophagosomes. Viruses were never present in proerythroblasts. There were few if any reticulum cells in the liver during the 4 days after infection. Several undifferentiated cells, possibly corresponding to the reticulum cells of Friend virus disease, were seen in the lumina of the sinusoids of the liver. Morphologically, these cells resembled primitive hemopoietic elements. These studies indicate that the liver and the spleen contribute to polycythemia in the early phase of Friend virus disease. (23 refs.)

78-0329 **Quantitation of Immature Granulocytic Cells in Peripheral Blood and Marrow of Mice with Friend Virus Induced Splenic Erythroleukemia (Meeting Abstract).** (Eng) Warren, W. (Div. Hematology, Peter Bent Brigham Hosp., Boston, MA); Greenberger, J. S.; Muse, M. *Clin Res* 25(5): 662A; 1977. (no refs.)

78-0330 **Lack of Erythroid Characteristics in Ia-positive Leukemia Cell Lines Induced by Friend Murine Leukemia Virus.** (Eng) Chesebro, B. (Rocky Mountain Lab., Natl. Inst. Allergy and Infectious Diseases, NIH, PHS, U.S. Dept. Health, Education, and Welfare, Hamilton, MT 59840); Wehrly, K.; Housman, D. *J Natl Cancer Inst* 60(1): 39-242; 1978.

Seventeen mouse leukemia cell lines induced by Friend murine leukemia virus (F-MuLV) were examined for cell membrane

antigens regulated by the I-region of the H-2 complex and for erythroid characteristics. Four of the lines were N-tropic, 12 were B tropic, 1 was NB tropic and 2 were possibly NB tropic. Erythroid traits tested were Hb synthesis, incorporation of  $^{59}\text{Fe}$  into heme before and after culture with dimethyl sulfoxide, and presence of globin messenger RNA. Thirteen lines were positive for erythroid characteristics and all these were Ia-negative; six were negative for erythroid characteristics and five of these were Ia-positive. The Ia-negative FBL-3 cell line showed no erythroid characteristics of any kind. These results suggest that Ia-negative F-MuLV-induced leukemias are erythroid in origin. FBL-3 could have been induced by the lymphatic helper virus of F-MuLV. The exact nature of the Ia-positive F-MuLV-induced cells is unknown; possible origins are discussed. (13 refs.)

78-0331 **Spontaneous Regression of Friend Virus-induced Erythroleukemia. III. The Role of Macrophages in Regression.** (Eng) Marcelletti, J. (Dept. Biology, Michigan Cancer Foundation, Detroit, MI 48201); Furmanski, P. *J Immunol* 120(1): 1-8; 1978.

The role of macrophages in the spontaneous regression of erythroleukemia induced by the regressing Friend virus (RFV) strain of FV was examined in leukemic Swiss mice. Elimination or suppression of macrophage function inhibited both in vitro and in vivo macrophage-dependent immune responses. Administration of agents cytotoxic for macrophages, such as silica, carrageenan, or antimacrophage serum, inhibited regression for the same period of time that each of them suppressed macrophage activity in vivo. Protection of macrophages against the action of silica or carrageenan with poly(2-vinylpyridine-N-oxide) abrogated the inhibition of regression caused by these agents. Macrophage phagocytic activity was inhibited in 50% of RFV-induced leukemic mice at 25-30 days after virus inoculation. Animals with normal macrophages regressed, whereas those with inhibited macrophages did not. Inhibited macrophages from leukemic mice were productively infected with virus, measured as infectious centers in an XC plaque assay. There was a correlation between the proportion of infected cells and the degree of inhibition of function in the population. The virus-infected cells are the cause of the decreased function, as shown by the fact that their removal results in the return of the phagocytic index to normal. Macrophages from regressor mice are neither functionally inhibited nor infected with virus. It is concluded that macrophages are a significant component in the host response leading to regression of FV-induced erythroleukemia. (23 refs.)

78-0332 **Proteolipids in Friend Leukemia Virus Infected Cells (Meeting Abstract).** (Fre) Audubert, F. (Groupe de Recherche #8 du C.N.R.S., Institut Gustave-Roussy, 94800 Villejuif, France); Semmel, M. *Biol Cellulaire* 30(1): 2a; 1977. (no refs.)



- 78-0333 Immunologic Control of the Ascites Form of Murine Adenocarcinoma 755. II. Tumor Immunity Associated with a Friend-Moloney-Rauscher-type Virus.** (Eng) Collins, J. J. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC 27710); Roloson, G.; Haagensen, D. E.; Fischinger, P. J.; Wells, S. A.; Holder, W.; Bolognesi, D. P. *J Natl Cancer Inst* 60(1): 141-152; 1978.

Ultrastructural analysis of AD755a cells growing in tissue culture or obtained from the ascitic fluid of C57BL/6J mice were found to contain a C-type virus (ADV), and the role of virus antigens in the serum transfer or rejection of this virus was investigated. Syngeneic mouse anti-AD755a antiserum could neutralize ADV, Friend murine leukemia virus (F-MuLV) and Rauscher murine leukemia virus and demonstrated group-specific reactivity for the major envelope glycoprotein (gp71) of murine leukemia virus (MuLV). Infectivity of AKR cell line MuLV or feline leukemia virus (FeLV) was not significantly reduced by the antiserum. The serum could also lyse mouse cells producing F-MuLV, but this reaction was only partially directed towards virus structural proteins: the immune transfer capacity could not be removed by antigens present in the intact virus preparation. Absorption with F-MuLV infected cells could eliminate the protective capacity of the anti-AD755a serum; absorption of cells expressing AKR MuLV or mammary virus antigens had no effect. Absorption with other tumor cell lines that expressed either B-type oncornavirus antigens or Gross-AKR gp71-like virus antigens did not remove the protective capacity of the serum. However, direct immunization of C57BL/6 mice with F-MuLV induced immunity to AD755a cells. It is suggested that virus structural antigens are involved in the induction of specific tumor immunity subsequent to direct immunization, and that virus-related cell surface antigens are responsible for the induction of antibodies mediating the protective capacity of the serum seen in passive transfer. Similar virion-associated antigens may be responsible for the immunologic characteristic of other transplantable tumors. (53 refs.)

- 78-0334 Properties of a P70 Proteolytic Factor of Murine Leukemia Viruses.** (Eng) Yoshinaka, Y. (Worcester Foundation Experimental Biology, Shrewsbury, MA 01545); Luftig, R. B. *Cell* 12(3): 709-719; 1977.

A P70 proteolytic factor of murine leukemia viruses such as Rauscher leukemia virus (RLV) was purified from JLSV-9 cells and characterized. P70 was separated from gp69/71 and shown to have the determinants of p30, p15, p12, and p10; it corresponds to the intracellular gag precursor polyprotein. Treatment of RLV with detergent releases a factor that cleaves P70; this factor is soluble and is present in a low concentration in virion preparations. It has a mol wt corresponding to 10,000 to 12,000 daltons, and it could be a minor species of p12. Upon cleavage of P70 with this factor, the amount of p40-42 remains constant, but the p30, p15, p12 and p10 polypeptide bands increase. Thus, in vitro cleavage mimicks in vivo cleavage. The cleavage pattern of P70-rich

immature cores treated with trypsin or chymotrypsin was different from that obtained with the P70 proteolytic factor. Thus, P70 proteolytic factor is a unique highly specific protease. P70 cleavage activity was blocked by tosylsulfonyllysyl chloromethyl ketone, p-tosyl-L-arginine methyl ester, N-carbobenzoxy (CBZ)-lysine, CBZ-lysine methyl ester, and phenylmethylsulfonyl fluoride (PMSF). The CBZ-lysine inhibition was reversible, but that of PMSF was irreversible. It is not known if P70 proteolytic factor is of viral or host origin. (33 refs.)

- 78-0335 Enhancement of Leukemogenesis in Mice after Prolonged Administration of Anti-interferon or Normal Rabbit Globulin.** (Eng) Ingnot, A. D. (Polish Acad. Science, Ludwik Hirsfeld Inst. Immunology and Experimental Therapy, ul. Czerska 12, 53-114 Wroclaw, Poland); Chudzio, T. *Arch Virol* 55(1/2): 67-75; 1977.

The prolonged administration of rabbit antimouse L-cell interferon globulin markedly potentiated Rauscher murine leukemia virus (MuLV) infection in BALB/c mice, as shown by spleen size. Normal rabbit globulin had a weaker, but still significant, augmenting effect on spleen enlargement. It was possible to discriminate quantitatively between the nonspecific enhancement of splenomegaly in MuLV-infected mice due to antigenic stimulation with normal rabbit globulin and the effects due to elimination of endogenous interferon by specific antibodies. The difference in spleen-enlarging activity between the antiinterferon IgG and normal rabbit IgG was max 3-4 wk after infection, when potent, diluted antiinterferon IgG (58 µg protein/dose) was used. Endogenous interferon, even when produced in undetectable amounts, apparently plays an essential role in controlling infection by an oncogenic virus. (21 refs.)

- 78-0336 Inhibition of Lymphocyte Transformation by Disrupted Murine Oncornavirus.** (Eng) Fowler, A. K. (Viral Oncology Program, NCI, Frederick Cancer Res. Center, Frederick, MD 21701); Twardzik, D. R.; Reed, C. D.; Weislow, O. S.; Hellman, A. *Cancer Res* 37(12): 4529-4531; 1977.

Freeze-thaw preparations of banded Rauscher murine leukemia virus markedly suppressed the in vitro cell-mediated blastogenic response of BALB/c AnN and C57BL/6N mouse splenic lymphocytes to phytohemagglutinin-P and to allogeneic cells in two-way mixed-WBC reactions. Suppression was shown not to be due to cytotoxicity or to virus-mitogen binding. It is suggested that a virion envelope component interferes with cell-mediated immunity by altering cell recognition sites. (12 refs.)

- 78-0337 Fatty Acid Components of Phospholipids in Rauscher Leukemia Cells (Meeting Abstract).** (Eng) Redai, I. (Inst. Microbiology, Univ. Medical Sch., Debrecen, Hungary); Biacs, P.; Kiss, J.; Toth, F. D. *Acta Microbiol Acad Sci Hung* 24(1): 75; 1977. (no refs.)



8-0338 **The Prognostic Importance of Plasma cAMP Level in Rauscher Leukemia (Meeting Abstract).** (Eng) Rethy, A. (Inst. Microbiology, Univ. Medical Sch., Debrecen, Hungary); Halmy, M.; Toth, F. D.; Kasa, M.; Vaczi, L. *Acta Microbiol Acad Sci Hung* 24(1): 74; 1977. (no refs.)

8-0339 **Rescue of a Transforming Virus from a Spontaneous Nonproducing Osteosarcoma in BALB/c Mice.** (Eng) Bentvelzen, P. (Radiobiological Inst. NO, 151 Lange Kleiweg, Rijswijk, ZH, Netherlands); Nooten, R.; Deys, B. F. *J Natl Cancer Inst* 60(2): 401-403; 1978.

Cultured cells from a spontaneous osteosarcoma, V793 of a 9-mo-old female BALB/c mouse did not produce a C-type oncovirus, as determined by extracellular reverse transcriptase assay and cytoplasmic immunofluorescence. However, after cocultivation with BALB/3T3 cells chronically infected with Rauscher murine leukemia virus (R-MuLV), a focus-forming virus was rescued that transformed BALB/3T3 cells, NIH/3T3 cells, and secondary BALB/c mouse embryo and WAG/Rij rat embryo fibroblasts. The transformation could be inhibited by antiserum to R-MuLV. (15 refs.)

8-0340 **Effects of Filipin on the Structure and Biological Activity of Enveloped Viruses.** (Eng) Majuk, (Dept. Chemistry, Queens Coll., City Univ. New York, Flushing, NY 11367); Bittman, R.; Landsberger, F. R.; Comans, R. W. *J Virol* 24(3): 883-892; 1977.

The interaction of the polyene antibiotic filipin with membrane-bound cholesterol in vesicular stomatitis (VS), influenza, and Rauscher leukemia virions was investigated. VS virions exposed to filipin had a series of depressions and ridges on the envelope with a periodicity of 15-20 nanometers (nm) perpendicular to the long axis of the particle; glycoprotein spikes were attached only to the ridges. A similar alteration was caused by filipin on trypsin-treated virions, which lacked surface glycoproteins. VS virions were occasionally found with 20 to 30-nm holes or depressions in the envelope. There were few alterations in the envelopes of influenza viruses, but Rauscher virions had circular pores similar to those seen in some VS virions. These changes were much different from those caused by amphotericin B treatment. Labeling of virions indicated that the filipin-induced alterations occur without dissociation of the viral membrane components. At cholesterol/filipin ratio of 0.21, there was approx a 500-fold reduction in VS virion infectivity; there was no appreciable reduction in influenza virion infectivity. Glycoproteins did not inhibit bonding of filipin to VS virions, but the initial rate of association of filipin with cholesterol was faster in protease-treated VS virions. A stoichiometry of approx 1 mole of bound filipin/mole cholesterol was found in both intact and protease-treated VS virions. The equilibrium dissociation

constant for filipin-cholesterol interaction was approx 74 times larger in intact than in protease-treated virions. The fluidity of lipids in VS viral membranes was markedly reduced when either intact or protease-treated virions were treated with filipin. (38 refs.)

78-0341 **Virus Infection of Murine Teratocarcinoma Stem Cell Lines.** (Eng) Teich, N. M. (Imperial Cancer Res. Fund Labs., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Weiss, R. A.; Martin, G. R.; Lowy, D. R. *Cell* 12(4): 973-982; 1977.

Three clonal murine teratocarcinoma stem cell lines were studied for susceptibility to infection by several different viruses. The sample included DNA-containing virus, vaccinia and RNA-containing viruses, encephalomyocarditis (EMC) virus, Sindbis virus, vesicular stomatitis (VS) virus, and murine leukemia virus (MuLV). In the undifferentiated state, the embryonal carcinoma stem cells are as sensitive to infection by EMC, Sindbis, vaccinia, and VS viruses as are embryo fibroblasts derived from the same mouse strain. The undifferentiated cells, unlike the fibroblasts, are entirely refractory to infection with MuLV. If the stem cells are allowed to differentiate, they become permissive for MuLV replication at a low level. In the one nullipotent cell line that did not differentiate either in vivo or in vitro, virus adsorption and penetration were not restricted, but an integrated proviral DNA copy could not be detected. In a pluripotent stem cell line, proviral DNA sequences were detected, but neither transcription into virus-specific RNA nor specific protein synthesis was observed. It is suggested that control of MuLV replication in the cells is a function of the stage of differentiation and, maybe, of the genetic composition of the teratocarcinoma stem cells. (45 refs.)

78-0342 **The Effect of Chronic Protozoan Infection by *Babesia rodhaini* on Leukemogenesis in Mice.** (Eng) Hugoson, G. (Natl. Veterinary Inst., Stockholm, Sweden); Lagerlor, B.; Thorell, B. *Int J Cancer* 20(6): 947-950; 1977.

The effect of chronic infection with the protozoan parasite *Babesia rodhaini* on the subsequent development of mouse leukemia was investigated in three murine lymphoma-leukemia model systems: (1) congenital thymic lymphoma in AKR mice; (2) radiation-induced thymic lymphoma in C57BL mice; and (3) Rauscher virus-induced leukemia in NMRI mice. There was no significant difference between *Babesia*-infected and uninfected AKR and C57BL mice at any time. Leukemia incidence was significantly greater in *Babesia*-infected NMRI mice that had been infected with an adjusted dose (1:10 dilution) of Rauscher leukemia virus than in controls. It appears that only at a certain level of viral leukemogenic action (virus level and dose) is there a synergism with chronic *Babesia* infection. These findings may par-



allel the observed positive correlation between bovine leukemia and chronic babesiosis as well as human epidemiological data about the connection between malarial infection and the development of Burkitt's lymphoma. (11 refs.)

- 78-0343 Density-dependent Changes in Hexose Transport, Glycolytic Enzyme Levels, and Glycolytic Rates, in Uninfected and Murine Sarcoma Virus-transformed Rat Kidney Cells.** (Eng) Gregory, S. H. (Natl. Inst. Arthritis, Metabolic, and Digestive Diseases, Building 10, Room 9B-11, Bethesda, MD 20014); Bose, S. K. *Exp Cell Res* 110(2): 387-397; 1977.

The relationship among hexose transport rate, glycolytic enzyme activity, and glycolytic rate was investigated in normal rat kidney (NRK) cells and Kirsten murine sarcoma virus-transformed (KNRK) cells grown under different culture conditions. Experiments with 2-deoxy-D-glucose (2-DG) transport indicated that the  $K_m$  was not affected by transformation or cell density;  $V_{max}$ , however, was affected by both. 2-DG transport was 5-25 times higher in KNRK cells. An increase in the cell density of KNRK cells had little effect on  $V_{max}$ , but an increase in NRK cell density caused a 3- to 6-fold decrease in  $V_{max}$ . Experiments with 3-O-methyl-D-glucose confirmed that these values reflected differences in transport and not metabolism. Increasing the volume of the medium had little effect on 2-DG transport by NRK cultures, but increasing the cell density had a marked influence on it: cells plated in a 78.5 cm<sup>2</sup> dish transported sugar approx three times faster than a similar number of cells in a dish with eight times less surface area. The degree of enhancement of glycolytic activity was also dependent on cell density. Hexokinase, phosphofructokinase, pyruvate kinase, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase activities were increased in dense KNRK cultures compared to sparse or uninfected cultures. Use of another virus-transformed cell line, ts339/NRK, indicated that the response of glycolytic enzymes to increased cell density was similar at 33 and 39 C; cells grown at 39 C also had a density-dependent inhibition of 2-DG transport. There was no correlation between glycolytic activity and lactate production in NRK or KNRK cells suggesting that enhanced growth and/or hexose transport are responsible for the increased lactate production in the transformed cells. (45 refs.)

- 78-0344 Correlation of In Vivo Cancer, Net Outer Charge, In Vitro Migration, Interferon Activity, In Vitro Growth Rates, and Chalone-like Activity to Transformation-Reversion in Cloned Moloney and Kirsten Sarcoma Virus-transformed Mouse 3T3 Cells.** (Eng) Ebbesen, P. (Inst. Medical Microbiology, Univ. Copenhagen, Copenhagen, Denmark); Olsson, L.; Rudkobing, O.; Haahr, S.; Kristensen, G. *Cancer Res* 37(12): 4285-4290; 1977.

The effect of malignant transformation and reversion on cell characteristics was studied in cloned Moloney and Kirsten sarcoma virus-infected, non-virus-producing mouse 3T3 cells (BALB cells and FL cells from Swiss mice). Only morphologically transformed cells induced tumors in vivo. Both transformed cell lines and one revertant FL cell line showed slower in vitro growth than uninfected cells, but the growth rates of the BALB 3T3 cells were unaffected by transformation-reversion. Transformation resulted in a less negative net outer charge. The charge normalized in revertant FL cells but not in revertant BALB 3T3 cells. In vitro migration for 24 hr in medium with or without fetal calf serum appeared to be unrelated to transformation. Interferon production after challenge with West Nile virus or Newcastle disease virus was enhanced in transformed and some revertant cells. Chalone-like DNA synthesis-inhibitory extracts (mol wt, 20,000-50,000) were prepared from cells and medium of all cultures, and each extract was tested on its cell of origin. No effect was found with cell extracts harvested from confluent cultures; however, extracts from subconfluent cultures inhibited DNA synthesis in all cells except Kirsten sarcoma virus-transformed BALB cells. In contrast to the cell extracts, the media extracts were more inhibitory when harvested from confluent than from subconfluent cultures. (23 refs.)

- 78-0345 Characterization of the Poly (A)+ and the Poly (A)- RNAs in the Native and Denatured Genomes of Oncornaviruses.** (Eng) Emanoil-Ravicovitch, R. (Laboratoire d'Hematologie Experimentale, Institut de Recherches sur les Maladies du Sang et les Leucemies, Hopital Saint-Louis, 75010 Paris, France); D'Auriol, L.; Robert, J.; Tavitian, A. *J Gen Virol* 37(3): 613-617; 1977.

The poly(A) (polyadenosine) content of the native and denatured 60 to 70S RNAs of mouse sarcoma virus (Moloney strain) (M-MSV(MLV)) from 78A<sub>1</sub> cells, Gross leukemia virus (GLV) from ERThrat cells, and simian sarcoma virus (SSV-1) from NRK rat cells was determined. In the native genome, a significant proportion of the poly(A)- RNA was present in the intact 60S to 70S RNA complex. The amount of poly(A)- RNA in the native genome was related to cellular growth and seemed to be independent of virus maturation. Following thermal denaturation, the subunits were approx 66% poly(A)+ and 33% poly(A)- RNA. The poly(A)- subunits were mainly composed of 20S to 28S RNA while the poly(A)+ subunits were mainly 30 to 35S RNA. Competitive molecular hybridization suggested that the two species possessed similar nucleotide sequences. It is also suggested that when optimal cellular growth conditions are not reached, some virus subunits lack poly(A) but are nevertheless assembled into virus particles forming a 60S to 70S RNA complex. (22 refs.)

- 78-0346 Functional Characterization of a Stable, Non-cytolytic Stage of Macrophage Activation in Tumors.** (Eng) Russell, S. W. (Dept. Immunopathology,



Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Doe, W. F.; McIntosh, A. T. *J Exp Med* 146(6): 1511-1520; 1977.

Macrophages (M $\phi$ ) from BALB/c mice with regressing Moloney sarcomas could kill tumor target cells within the first 24 hr in vitro. Thereafter, regressor M $\phi$  were noncytolytic. M $\phi$  from several different progressing sarcomas failed to kill, even when challenged with target cells immediately after explantation. Similarly, thioglycollate-induced peritoneal M $\phi$  (TG-M $\phi$ ) did not kill. Noncytolytic M $\phi$  derived from progressing sarcomas or from long-term (up to 96 hr) cultures of regressor M $\phi$  were highly sensitive to stimulation by bacterial lipopolysaccharide (LPS): even picogram per milliliter amounts induced killing. Similar concentrations of LPS had no demonstrable effect on TG-M $\phi$ . Thus, tumor M $\phi$  generally appeared to have been primed in vivo, with those in regressing sarcomas having additionally acquired cytolytic activity. The inability of progressor M $\phi$  to kill apparently stemmed from their failure to respond to the signal needed in vivo to trigger cytolytic activity, rather than to the total absence of activation. (17 refs.)

**78-0347 Immunization of Mice with Syngeneic Moloney Lymphoma Cells Induces Separate Antibodies Against Virion Envelope glycoprotein and Virus-induced Cell Surface Antigens.** (Eng) Fenyo, E. M. (Dept. Tumor Biology, Karolinska Inst., Stockholm 60, Sweden); Yefenof, E.; Klein, E.; Klein, G. *J Exp Med* 146(6): 1521-1533; 1977.

Immunization of (A x C57BL)F<sub>1</sub> or (A x C57L)F<sub>1</sub> mice with heavily irradiated syngeneic Moloney lymphoma cells (YAC) evoked antibodies against the major viral envelope antigen, gp71, and the Moloney virus-induced cell surface antigen (MCSA). A9HT cells, an L-cell subline, reacted with the antibodies against the viral envelope antigen only; this reaction could be completely inhibited by virus or purified gp71. The reactivity to YAC was only partially inhibited (max 30%) or not at all. This was attributed to reaction of the YAC cells with antibodies directed against MCSA, a nonvirion cell surface component according to both biological and biochemical evidence. Antibody-induced capping of gp71 or p15(E) did not change the membrane distribution of MCSA or H-2, indicating that these antigens represent distinct entities on the cell surface. MCSA showed only minimal capping and thereby differed in behavior from both H-2 and virion antigens. Capping of gp71 was induced by the mouse antiserum, as revealed by subsequent staining with monospecific anti-gp71 antiserum. Under ordinary test conditions, this reactivity is overshadowed by the reaction against MCSA. The lack of MCSA capping reflects a difference in the anchorage of this antigen. (26 refs.)

**78-0348 Germ Line Integration of Moloney Leukemia Virus: Effect of Homozygosity at the M-MuLV Locus.** (Eng) Jaenisch, R. (Heinrich-Pette-Institut für experimentelle Virologie, Universität Hamburg, Martinstrasse

52, 2000 Hamburg 20, W. Germany). *Cell* 12(3): 691-696; 1977.

The role of homozygosity in the normal development of mice genetically transmitting Moloney leukemia virus (M-MuLV) was investigated. Hybridization of M-MuLV complementary DNA (cDNA) to liver DNA of heterozygous animals revealed an av of 1.2 copies of M-MuLV per diploid mouse genome equivalent; the corresponding figure for the DNA of leukemic spleens was 5.7 copies per genome. Embryos of heterozygous animals [female (+-) x male (+-)] revealed three classes of M-MuLV DNA annealing with cDNA; the first class carried two copies of M-MuLV-specific sequences per genome, the second one copy, and the third no M-MuLV specific sequences. In further mating experiments, the offspring were allowed to survive, and hepatectomy was performed at 6 to 8 wk. The same three classes of offspring were noted in a ratio of approx 1:2:1; all animals were viremic, having been infected congenitally by the mother. Mating of the F<sub>1</sub> generation revealed that transmission followed classical Mendelian formulas. These results indicate that homozygosity at the M-MuLV locus has no detectable effect on normal development. A mouse colony of animals homozygous at the M-MuLV locus was established. (25 refs.)

**78-0349 Relationship Between Nucleic Acids Associated with Intracytoplasmic A Particles and Mouse Mammary Tumour Virus RNA.** (Eng) Michalides, R. (Netherlands Cancer Inst., Div. Virology, Sarphatistraat 108, Amsterdam, Netherlands); Nusse, R.; Smith, G. H.; Zotter, S.; Muller, M. *J Gen Virol* 37(3): 511-521; 1977.

Molecular hybridization techniques were used to study the relationship between the RNA and DNA of intracytoplasmic A particles (IAP) of several origins and the mouse mammary tumor virus (MTV) genome. IAP from mammary tumor tissue had a buoyant density of 1.26 g/ml and demonstrated a RNA-directed DNA polymerase with a cation preference similar to that of MTV. Hybridization experiments indicated that the RNA of IAP was homologous to the RNA of MTV. DNA of IAP was not a replicative form of the MTV genome because no hybridization was observed between the IAP DNA and labeled RNA or complementary DNA of MTV. The significance of these findings, in relation to other findings in the literature, is discussed. (24 refs.)

**78-0350 Oncogenicity of Murine Mammary Tumor Virus Produced in Tissue Culture: Brief Communication.** (Eng) Arthur, L. O. (Viral Oncology Program, NCI Frederick Cancer Res. Center, P. O. Box B, Frederick, MD 21701); Fine, D. L.; Bentvelzen, P. *J Natl Cancer Inst* 60(2): 461-464; 1978.

A murine mammary tumor virus (MuMTV) produced by a glucocorticoid-stimulated C3H mouse mammary adenocar-



cinoma cell line, was free of murine leukemia virus and oncogenic for weaning BALB/c mice. Adenocarcinomas were induced by MuMTV as early as 136 days postinoculation and with as few as  $5 \times 10^3$  virus particles/mouse. Tumor incidence did not correlate directly with virus dose; it was low at higher MuMTV concentrations ( $1.2 \times 10^4$  particles/mouse), reached an optimum at  $1.3 \times 10^3$  particles/mouse, and decreased with virus dilution. (34 refs.)

- 78-0351 Evidence for an Influence of Mammary Tumour Virus on Prolactin Secretions in the Mouse.** (Eng) Sinha, Y. N. (Lutcher Brown Center for Diabetes and Endocrinology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Salocks, C. B.; Vanderlaan, W. P.; Vlahakis, G. *J Endocrinol* 74(3): 383-392; 1977.

Serum prolactin levels were studied in the Heston and Strong substrains of C3H/He and C57BL/He mice, which are positive and negative, respectively, for the milk-borne mammary tumor virus (MTV). In the MTV-positive C3H mice of both substrains, basal and perphenazine-induced prolactin levels were substantially lower than those in the MTV negative C57BL substrains. Foster nursing of C3H mice by C57BL dams and vice versa significantly altered this characteristic pattern of prolactin secretion. A brief preexposure of C3H young to their own mothers' milk virtually abolished the effect of foster nursing. The results show that the strain of the nursing mother markedly influences prolactin secretion in the adult, and they suggest that milk-borne MTV may have a role in prolactin secretion regulation in some mouse strains. The foster nursing-induced differences in serum prolactin secretion were unrelated to the amount of prolactin depleted from the pituitary gland, which implies that the metabolism of this hormone differs in MTV-positive and -negative strains. (22 refs.)

- 78-0352 Radioimmunoassay for Glycoprotein gp47 of Murine Mammary Tumor Virus in Organs and Serum of Mice and Search for Related Antigens in Human Sera.** (Eng) Zangerle, P. F. (Laboratoire de Radioimmunologie, Univ. Liege, Liege, Belgium); Calberg-Bacq, C. M.; Colin, C.; Franchimont, P.; Francois, C.; Gosselin, L.; Kozma, S.; Osterrieth, P. M. *Cancer Res* 37(12): 4326-4331; 1977.

The major murine mammary tumor virus (MuMTV) glycoprotein (gp47), prepared by diethylaminoethyl cellulose and hydroxyapatite chromatography of the detergent-mercaptoethanol-KCl-disrupted virion, was used as labeled antigen in a highly specific and reproducible radioimmunoassay. Seven other (glyco) proteins were antigenically distinct from gp47. The serum and organs of uninfected C57BL mice did not contain gp47, but the antigen was present in the sera of infected Swiss and RIII mice. Despite the high content in the mammary gland, gp47 levels in other organs was identical

in male and female mice. The serum titer gp47 was high in tumor-bearing females, but it varied with the mouse strain. Anti-gp47 immunoglobulins could not be detected. Of 314 human sera (107 normal, 65 benign mastopathy, 89 breast cancer, and 53 digestive cancer) analyzed, none contained an antigen related to gp47. One of 20 human mammary cyst fluids was positive. (21 refs.)

- 78-0353 Increased Incidence of Mammary Gland Tumors in Rats Infected with Murine Bittner Virus.** (Rus) Gruntenko, E. V. (Inst. Cytology and Genetics, Novosibirsk, USSR); Matiyenko, N. A. *Dokl Akad Nauk SSSR* 237(4): 987-989; 1977.

In a study designed to evaluate the possible effect of Bittner murine tumor virus (MTV) on mammary gland tumorigenesis, newborn Sprague-Dawley rats were inoculated sc with a MTV-containing extract from spontaneous mammary gland tumors of C3H/He mice (0.05 ml on day 1 and a 0.1 ml on days 2 and 4). Animals were divided into four groups: Group 1 rats served as controls, Group 2 rats were inoculated with MTV, Groups 3 rats were thymectomized, Group 4 rats were inoculated with virus and thymectomized. Thymectomy (at age 3 days) was performed to test the hypothesis that immunodepression may help to surmount the species barrier. The animals were followed-up for at least 900 days. The incidence of spontaneous mammary gland tumors in Group 1 was 22%; early thymectomy increased tumor frequency significantly to 36.4% in Group 3. However, infection with MTV also increased tumor incidence even higher, to 41.4% in Group 2 and 60.0% in Group 4. Thymectomy reduced the latent period from 706 days in Group 2 to 609 days in Group 4. (7 refs.)

- 78-0354 Suppressor Cells in Mice with Murine Mammary Tumor Virus-induced Mammary Tumors. I. Inhibition of Mitogen-induced Lymphocyte Stimulation.** (Eng) Rudeczynski, A. B. (Dept. Biology, Michigan Cancer Foundation, Meyer L. Prentis Cancer Center, 110 E. Warren Ave., Detroit, MI 48201); Mortensen, R. F. *J Natl Cancer Inst* 60(1): 205-211; 1978.

Investigations were conducted to determine whether a suppressor lymphoid population was present in C3H/HeN mice with murine mammary tumor virus (MuMTV)-induced mammary tumors. Suppressor cell activity was detected, and these cells effectively suppressed the blastogenic response of syngeneic normal lymphocytes to concanavalin A (Con A). Suppression was not dependent on DNA synthesis. Removal of the suppressor cells from spleen cell suspensions of tumor-bearing animals by passage of the cells on glass wool columns increased the Con A response of the remaining cells by four- to eight-fold. The cells also contained a significantly increased proportion of surface immunoglobulin-bearing and complement receptor-bearing lymphocytes. The cells could not be fractionated on plastic. Characterization experiments



suggested that the suppressor cells have B cell properties but not macrophage or T cell properties. The effect of these suppressor cells on host-tumor interaction has not been established. (29 refs.)

**78-0355 Oncornaviruslike Particles in the Cochlear Spiral Ganglion of Guinea Pigs.** (Ger) Merck, W. (Universitäts-HNO-Klinik, D-7800 Freiburg im Breisgau, W. Germany); Kistler, G. S.; Riede, U. N.; Lohle, E.; Sanritter, W. *Beitr Pathol* 161(2): 142-149; 1977.

Twenty guinea pigs from four different breeds (one being a specific pathogen-free line) were examined for histological abnormalities and antibodies to polyoma, Sendai, simian, and lymphocytic choriomeningitis virus. Histologically, all animals were free of abnormalities. However, the spiral ganglia of all four breeds showed intracytoplasmic viruses in some of the granular cells. On the basis of their morphology they were classified as oncornaviruses. There was an accumulation of lysosome-like vacuoles in the vicinity of the viruses, indicating an increase in local lysosomal activity in the infected cells. The rest of the ultrastructure of the infected cells appeared normal. Apparently, there is a worldwide latent viral infection in guinea pigs. (16 refs.)

**78-0356 Analysis of Polyribosomes and Intracellular RNA from Feline Leukemia Virus Infected Cells (Meeting Abstract).** (Eng) Conley, A. J. (Michigan State Univ., East Lansing, MI). *Diss Abstr Int [B]* 38(5): 041B-2042B; 1977. (no refs.)

**78-0357 Reiteration Frequency of Feline Type C Viral Genomes in Homologous and Heterologous Host Cell DNA.** (Eng) Okabe, H. (Viral Oncology Program, NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701); DuBuy, J.; Hatanaka, M.; Gilden, R. V. *Interferology* 9(4): 253-260; 1978.

Differences in the multiplicity of proviral sequences of two feline endogenous viruses, RD-114 and feline leukemia virus (FeLV) in homologous and heterologous DNA were examined by viral complementary DNA (cDNA) hybridization using cellular DNA fractionated with respect to reiteration frequency. Hybridization of the Theilen strain of FeLV (T-FeLV) <sup>3</sup>H-DNA probe with normal cat DNA indicated that the viral probe hybridized with intermediate-repeated DNA sequences to the same extent as with total DNA. Thus the viral DNA in these fractions shares the same sequences. A similar pattern was observed with RD-114 <sup>3</sup>H-DNA and cat liver DNA. When the RD-114 <sup>3</sup>H-DNA probe was hybridized with fractionated DNA from the human cell line RD-114, the curve mimicked that of total DNA. Thus, the viral genome of RD-114 virus is apparently fractionated with the

unique-sequence DNA of the exogenously infected human cells. It is estimated that the multiplicity of viral genomes in cat liver is about 7 and 24 per haploid genome for FeLV and RD-114, respectively. With RD-114 cells, however, the multiplicity is about four to five copies per haploid genome. (13 refs.)

**78-0358 Bvr-1, A Restriction Locus of a Type C RNA Virus in the Feline Cellular Genome: Pleiotropic Restriction of Endogenous BALB Virus in Cat Mouse Somatic Cell Hybrids.** (Eng) O'Brien, S. J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Simonson, J. M. *J Exp Med* 147(1): 219-232; 1978.

The pleiotropic action of the dominant X-linked feline gene *Bvr-1* on N-, B-, and X-tropic BALB/c retroviruses in feline FL-74 (from a renal lymphoma) x murine RAG (renal adenocarcinoma) somatic cell hybrids was investigated. *Bvr-1* restricts the replication of B-tropic murine leukemia virus (B-MuLV) in these hybrids. These cells were selected to obtain hybrids that had lost the feline X-chromosome on which was located the structural gene for hypoxanthine-guanine phosphoribosyl transferase and *Bvr-1*. Back-selected *Bvr-1* cells expressed high parental levels of B-MuLV. *Bvr-1* effectively restricted the iododeoxyuridine-mediated induction of the endogenous x-tropic BALB virus, but not the endogenous N-tropic virus. Pleiotropic restriction of B-MuLV and X-MuLV, but not N-MuLV, suggests that the viral targets of *Bvr-1* of the B-tropic and X-tropic endogenous BALB viruses are similar to each other but distinct from the target in the N-tropic virus. Low levels of B-MuLV were detected in restricted cells, but this residual virus was not infectious in either NIH-3T3 or BALB-3T3 mouse cells (*Fv-1N/Fv-1BV* and *Fv-1B/Fv-1B*, respectively). Passage of residual virus through host cells without *Fv-1*-related restriction resulted in the production of infectious B-MuLV indistinguishable from that produced by RAG parent cells. (37 refs.)

**78-0359 Lysis of Feline Lymphoma Cells by Complement-dependent Antibodies in Feline Leukemia Virus Contact Cats. Correlation of Lysis and Antibodies to Feline Oncornavirus-associated Cell Membrane Antigen.** (Eng) Grant, C. K. (Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA 02115); Essex, M.; Pedersen, N. C.; Hardy, W. D.; Stephenson, J. R.; Cotter, S.; Theilen, G. H. *J Natl Cancer Inst* 60(1): 161-166; 1978.

Samples of sera were collected from 346 healthy cats, cats exposed to feline leukemia virus (FeLV) infection and sick cats, and tested for lytic antibodies and antibodies to feline oncornavirus-associated cell membrane antigen (FOCMA). In both assays, FL74, a cat lymphoblastoid cell line which replicates FeLV, was used as a target. Correlation of presence or absence of antibodies detected by both tests was 91% overall and 100% for 93 samples containing lytic antibody at a



titer of -1:25 and anti-FOCMA antibodies at a titer of -1:16. Complement-dependent antibodies (CDA) and anti-FOCMA antibodies were detected in sera from viremic cats; these sera did not contain detectable antibodies to either the major envelope or core proteins of FeLV (gp70 and p30), or to the endogenous cat oncornavirus RD114. Immune sera that lysed FL74 cells also lysed F422 cells which only replicated A-subgroup viruses. Infectious virus particles could frequently be isolated from these sera. CDA were detected in sera from laboratory bred normal cats only after contact exposure to cats infected with FeLV; lytic antibodies appeared between 8 and 32 wk after exposure, coinciding with the first evidence of virus infection in blood smears. High antibody titers were maintained regardless of the persistence of infection. CDA were found in approx 2% of the sera from cats maintained in FeLV-free environments, 25% of sera from a randomized sampling of privately owned cats, 36% to 45% of sera from virus-infected cats of leukemia-cluster households and 8% of sera from cats with leukemia or lymphoma. Exposure of cats to horizontal FeLV infection induced antibodies that lysed cat lymphoma cells with cat complement; these antibodies were similar to anti-FOCMA antibodies, which have a proven antitumor and immune surveillance function in vivo. (29 refs.)

- 78-0360 Inhibition of Concanavalin A Stimulation of Feline Lymphocytes by Inactivated Feline Leukemia Virus.** (Eng) Hebebrand, L. C. (Dept. Veterinary Pathology, Coll. Biological Sciences, Ohio State Univ., Columbus, OH 43210); Mathes, L. E.; Olsen, R. G. *Cancer Res* 37(12): 4532-4533; 1977.

In a lymphocyte blast transformation assay, the response of feline lymphocytes to concanavalin A (Con A) was suppressed 20%-65% in the presence of inactivated feline leukemia virus. The decrease was not due to viral cytotoxicity, as determined by trypan blue viability counts, nor did the virus bind to Con A and interfere with its mitogenic stimulation. The virus may be biochemically repressive in itself, interfering with cell-mediated immunity within the feline system. (10 refs.)

- 78-0361 Inhibition of Bovine Leukemia Virus Release by Antiviral Antibodies.** (Eng) Driscoll, D. M. (Dept. Veterinary Science, Univ. Wisconsin, 1655 Linden Drive, Madison, WI 53706); Onuma, M.; Olson, C. *Arch Virol* 55(1/2): 139-144; 1977.

Peripheral blood lymphocytes from bovine leukemia virus (BLV)-infected cattle were grown in vitro with sera from BLV-infected and uninfected cattle, sheep, and rabbits. Only sera from infected animals that had antibody to gp 45/55, the major glycoprotein antigen, inhibited virus release from the cells. Although viral antigens were detected in the cells, none were detected in the supernatants of cultures grown

with these sera. Normal sera and sera with antibody only to p23, the internal BLV antigen, did not inhibit virus release. To identify the factor responsible for virus release inhibition, two inhibitory sera were absorbed with gp 45/55, p23, or tissue culture cells from BLV-infected and uninfected cell lines. The results indicated that antibody to gp 45/55 is the factor responsible for virus release inhibition. (10 refs.)

- 78-0362 Location of Antigens Associated with Bovine Leukemia Virus.** (Eng) Onuma, M. (Dept. Veterinary Science, Univ. Wisconsin, 1655 Linden Drive, Madison, WI 53706); Driscoll, D. M.; Olson, C. *Arch Virol* 55(1/2): 131-137; 1977.

Antigens associated with bovine leukemia virus (BLV) infection (gp 44/55 and p23) were identified by neutralization and immunofluorescent antibody (FA) tests. Only sera containing antibody to gp 45/55 neutralized the virus; antibody to p23 did not. These results indicate that gp 45/55 may be located in the virus envelope. In indirect fluorescent antibody (FA) tests, a cytoplasmic fluorescence and a membrane fluorescence were detected in BLV-infected cells. The serum used in the FA test was then absorbed with either p23 or gp 45/55. The results suggest that the membrane fluorescence is associated with gp 45/55 and that cytoplasmic fluorescence is associated with p23. (22 refs.)

- 78-0363 A Reverse Transcriptase Assay for Detection of the Bovine Leukemia Virus.** (Eng) Graves, D. C. (Comparative Leukemia Studies Unit, New Bolton Center, Univ. Pennsylvania, Kennett Square, PA 19348); Diglio, C. A.; Ferrer, J. F. *Am J Vet Res* 38(11): 1739-1744; 1977.

An RNA-dependent DNA polymerase or reverse transcriptase was demonstrated in highly purified bovine leukemia virus (BLV) particles. The viral enzyme responded effectively to the exogenous template primer polynucleotide (poly) (rA)-oligonucleotide (oligo) (dT). Unlike the reverse transcriptases of most mammalian C-type RNA viruses and of bovine syncytial virus, the BLV enzyme preferred magnesium rather than manganese for optimal activity. The identification of several other prerequisites for optimal reverse transcriptase activity led to the development of a rapid, semiquantitative assay, for the detection of BLV in supernatant fluids of monolayer cell cultures. However, the assay is not sufficiently reproducible for the routine detection of BLV in short-term cultures of bovine peripheral blood lymphocytes. Therefore, it is unsuitable for the diagnosis of BLV infection in cattle. (45 refs.)

- 78-0364 Epidemiologic Study on Enzootic Bovine Leukemia Using Serologic Tests and Hematologic Examinations.** (Eng) Rutili, D. (Istituto Zooprofilattico



perimentale dell'Umbria e delle Marche, Perugia, Italy);  
everini, M.; Rampichini, L.; Titoli, E.; Chicchini, U. *Tumori*  
3(5): 407-413; 1977.

hematologic, serologic, and electron microscopic examina-  
tions were performed on 262 Friesian dairy cattle to deter-  
mine the most suitable procedures for detecting animals in-  
fected with bovine leukemia virus (BLV). Immunodiffusion  
(ID) tests were performed with two different precipitating  
antigens: (1) those prepared from permanently infected  
monolayer cultures of fetal bovine lung cells (FBLV-Ag); and  
(2) antigens prepared from a glycoprotein of mol wt 58,000  
(gp58-Ag). Complement fixation (CF) and immunofluores-  
cence (IF) tests were also made. The greatest degree of corre-  
lation was seen between ID/gp58 and CF (82.7%) and be-  
tween ID/gp58 and IF (72.7%). There was little correlation  
between ID/FBLV and the other serologic tests. The ability  
to demonstrate antibodies in carriers of BLV appeared excel-  
lent with IF and ID/gp58, good with CF, but insufficient  
with ID/FBLV. In an epidemiologic investigation of enzootic  
bovine leukemia, the ID/gp58 and IF tests should be used  
in conjunction with hematologic examinations. (24 refs.)

**78-0365 Characterization of Mason-Pfizer Virus In-  
duced Cell Transformation In Vitro.** (Eng)

Ahmed, M. (John L. Smith Memorial for Cancer Res., Pfizer  
Inc., 199 Maywood Ave., Maywood, NJ 07607); Yeh, J.;  
Tolden, H. E.; Korol, W.; Schidlovsky, G.; Mayyasi, S. A.  
*Arch Virol* 55(1/2): 93-105; 1977.

Following infection with Mason-Pfizer monkey virus (M-  
PMV), several cell strains and established cell lines of simian  
and human origin failed to demonstrate foci of altered cells.  
However, most diploid cultures, after infection, lived longer  
and displayed the ability to grown in soft agar. The number  
of cell colonies developing in soft agar was directly propor-  
tional to the amount of virus added to the culture. Two types  
of cell colonies were isolated from soft agar after infection  
of monkey foreskin cells with M-PMV. One had a character-  
istic fibroblastic morphology and the other showed an epi-  
thelioid cell phenotype. The ratio of fibroblastic colonies to  
epithelioid colonies was > 20:1. The epithelioid cultures dis-  
played a complete lack of topoinhibition, formed three-  
dimensional cellular dome structures, and demonstrated sig-  
nificant karyotypic alterations. Fibroblastic sublines, on the  
other hand, did not form domes, but they did show some lack  
of topoinhibition. Most cells in the fibroblastic sublines also  
continued to show a normal rhesus chromosome comple-  
ment. Although both epithelioid and fibroblastic transformed  
cells produced intracellular M-PMV antigen and virus parti-  
cles, the infectious virus titers were significantly different.  
The noninfectious virus preparations recovered from some of  
the fibroblastic sublines contained a high percentage of aber-  
rant forms of M-PMV. (17 refs.)

**78-0366 Uncoating and Gene Expression of Simian  
Virus 40 in CV-1 Cell Nuclei Inoculated by Mi-**

**croinjection.** (Eng) Diacumakos, E. G. (Rockefeller Univ.,  
New York, NY 10021); Gershey, E. L. *J Virol* 24(3): 903-906;  
1977.

Simian virus 40 (SV40) virions were microinjected into the  
nucleus and cytoplasm of CV-1 cells to determine whether  
uncoating of the virus is a wholly nuclear event or whether  
prior interaction with the cell surface, transport through the  
cytoplasm, or fusion of the vesicles containing virus with the  
nuclear envelope is also necessary. The virus preparation con-  
tained complete virions. The inocula for the nuclear injec-  
tions contained 0.04 infectious unit (an av of 1 virus particle)  
in  $2 \times 10^{-10}$  cells/ml; the inocula for the cytoplasmic injections  
were twice as large, containing an av of two virus particles.  
Analysis 48 hr later indicated that 18/30 cells receiving nu-  
clear injections and 3/30 receiving cytoplasmic injections had  
T-antigen production. Thus, interaction with the cell surface  
and transport through the cytoplasm and nuclear envelope  
are not necessary for uncoating of SV40 and T-antigen syn-  
thesis. Also, the high particle: plaque-forming unit ratios used  
to infect cells are due to the inefficiency of virus adsorption  
and transport and not to defective virions. (14 refs.)

**78-0367 Regulatory Function of Simian Virus 40 DNA  
Replication for Late Viral Gene Expression.**

(Eng) Graessmann, A. (Institut für Molekularbiologie und  
Biochemie der Freien Universität Berlin, West Berlin 33, Ar-  
nimallee 22, W. Germany); Graessmann, M.; Mueller, C.  
*Proc Natl Acad Sci USA* 74(11): 4831-4834; 1977.

Late viral gene expression was studied in TC7 cells inoculated  
with simian virus 40 (SV40) DNA and SV40 replicative inter-  
mediates (RI). SV40 native superhelical DNA (DNA I) and  
RI-DNA, at a concentration of 0.1 mg/ml, induced T- and  
V-antigen synthesis in all recipient cells, but SV40 DNA I  
could not induce V-antigen synthesis if DNA synthesis was  
halted. In the absence of DNA synthesis, about 30% of the  
cells inoculated with RI-DNA had strong V-antigen-specific  
fluorescence 24 hr later. Nicked circular (form II) and dou-  
ble-strand linear (form III) SV40 DNA induced T- and V-  
antigen synthesis but failed to induce V-antigen synthesis  
in the presence of cytosine arabinoside. Nonpermissive 3T3  
mouse cells microinoculated with 200 to 400 SV40 DNA I  
molecules/recipient supported early but not late viral gene  
expression. RI-DNA induced V-antigen synthesis in 28% of  
the inoculated 3T3 cells with or without inhibitors of DNA  
synthesis. V-antigen synthesis was obtained by injection of  
a temperature-sensitive mutant A7 RI-DNA preparation at  
41.5°C; SV40 DNA I at a tenfold higher concentration failed  
to induce V-antigen synthesis. (26 refs.)

**78-0368 Immunologic Selection Against Simian Virus-  
40 Transformed Cells: Concomitant Loss of Vi-  
ral Antigens and Early Viral Gene Sequences.** (Eng) Kuster,



J. M. (Macromolecular Biology Section, Immunology Program, NCI, NIH, Bethesda, MD 20014); Mora, P. T.; Brown, M.; Khoury, G. *Proc Natl Acad Sci USA* 74(11): 4796-4800; 1977.

A highly tumorigenic, spontaneously transformed mouse embryo cell line was cloned, the resulting T AL/N clone 3 cells were infected with simian virus 40 (SV40) at a multiplicity of 360 plaque-forming units per cell, and the cells were subsequently recloned. Subclone I of the SV40-transformed cells expressed SV40-specific T (nuclear) and transplantation antigens, but it was 100 times less tumorigenic than the parent T AL/N clone 3 cells. When  $10^4$  to  $10^5$  subclone I cells were injected into syngeneic AL/N mice, tumors were produced. Cell lines were established from the tumors, all of which were consistently negative for T antigen. All tumor lines tested were found not to contain SV40-specific transplantation antigen, and they had again become highly tumorigenic. The original subclone I cells contained about one copy of SV40 DNA per diploid amount of cell DNA, as well as RNA complementary to the early region of the SV40 genome. The T-antigen-negative cells from one tumor line contained approx 0.5 copy of SV40 DNA per diploid equivalent and did not synthesize any detectable virus-specific RNA. Reassociation kinetic analysis demonstrated that the cells of this line and its clones had lost DNA sequences predominantly from the early region of the SV40 genome. Thus, stably integrated SV40 DNA sequences can be present in a cell without the expression of viral antigens. (31 refs.)

**78-0369 Asymmetric Okazaki Piece Synthesis During Replication of Simian Virus 40 DNA In Vivo.**

(Eng) Perlman, D. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA 02139); Huberman, J. A. *Cell* 12(4): 1029-1043; 1977.

The hybridization of Okazaki pieces (DNA chains < 250 nucleotides long found during replication) and simian virus 40, (SV40) intermediate-sized DNA to the Hind II+III-A and Hpa II-Eco RI-B SV40 restriction fragments was determined in BSC-1 cells. The SV40 fragments were chosen because they lie on either side of the origin of bidirectional DNA replication. As much as five times more Okazaki piece DNA hybridized to the strand oriented in the 3'-5' direction away from the replication origin (the strands expected to be synthesized discontinuously). Neither the duration of the labeling period nor the temperature of the cells during labeling significantly altered this hybridization asymmetry. Thymine asymmetry was negligible, based on the H:P ratio. When hybridization of the intermediate-sized strand was considered, a reverse asymmetry was noted: 5'-3' up to 1.7 times more hybridization occurred in the strands oriented away from the origin of replication. After 30 min preincubation with fluorodeoxyuridine, a heterogeneous low-mol wt DNA with no hybridization asymmetry was found. After 15 min preincubation, a similar heterogeneous peak of low-mol wt DNA was found, but synthesis of the intermediate-sized DNA was not inhibited

completely. The size distribution of the Okazaki piece DNA from each strand was the same: wt av approx 145 nucleotides, max size 200-250 nucleotides. This indicated that the asymmetry resulted from a difference in the number of pieces in each strand, rather than their size. It is concluded that the SV40 DNA is synthesized semidiscontinuously: the strand of 3'-5' orientation away from the origin is synthesized in short Okazaki pieces that are subsequently joined together and the 5'-3' strand is synthesized continuously. (31 refs.)

**78-0370 Oncogenicity of SV40 DNA in the Syrian Hamster.** (Eng) Sol, C. J. (Laboratorium voor de Gezondheidsleer, Universiteit van Amsterdam, Mauritskade 57, Amsterdam-O, Netherlands); van der Noordaa, J. *J Gen Virol* 37(3): 635-638; 1977.

The oncogenicity of simian virus 40 (SV40) DNA in syrian hamsters was characterized. Purified SV40 DNA with an infectivity of  $1.5 \times 10^6$  plaque forming units (PFU)/ $\mu$ g added in 0.5 ml cultures of primary rat kidney resulted in a transformation-efficiency of 25 foci/ $\mu$ g DNA. Sc injection of 1 or 2  $\mu$ g DNA into newborn hamsters resulted in tumor growth in 11/33 hamsters. The one tumor studied histologically was a sarcoma; study of cells from the sixth culture passage revealed T antigen in 95% of the cells. Virus rescued from cultured cells had the same cleavage pattern as the injected virus DNA. Treatment of the inoculum with DNase resulted in no tumor growth. Neither calf thymus DNA nor poly-L-ornithine enhanced the infectivity. Cleavage of the DNA by EcoRI did not affect in vitro transforming potential. (13 refs.)

**78-0371 Early and Late Messenger RNA of SV40: Physical Cartography and Regulation of Transcription (Meeting Abstract).** (Fre) May, E. (Institut de Recherches Scientifiques sur le Cancer, 94 800 Villejuif, France). *Biol Cellulaire* 29(2/3): 52a; 1977. (no refs.)

**78-0372 The SV40 Transcription Complex. I. Effect of Viral Chromatin Proteins on Endogenous RNA Polymerase Activity.** (Eng) Brooks, T. L. (Dept. Biology, Univ. California, San Diego, La Jolla, CA 92093); Green, M. H. *Nucleic Acids Res* 4(12): 4261-4277; 1977.

Simian virus 40 (SV40) chromatin obtained from infected monkey cells was used to study the effect of viral chromatin proteins on endogenous RNA polymerase II. Reaction conditions were sought that would generate high mol wt SV40 RNA at a max rate while retaining the association of protein with the bulk of the viral DNA in the preparation. Ammonium sulfate activated the rate of transcription by endogenous RNA polymerase in two ways: (1) by direct action on the



zyme; and (2) by causing a reversible conformational change in the viral chromatin. Under optimal reaction conditions (0.3 M ammonium sulfate), the viral chromatin proteins did not limit the rate of RNA chain elongation, and high molecular RNA ( $1.6 \times 10^6$  daltons) was synthesized by the SV40 chromatin. It is postulated that the conformational changes in the chromatin structure that are stimulated by the high salt concentration permit endogenous RNA polymerase to transcribe chromatin as rapidly as free DNA. (36 refs.)

- 78-0373 **The SV40 Transcription Complex. II. Non-dissociation of Protein from SV40 Chromatin during Transcription.** (Eng) Green, M. H. (Dept. Biology, Univ. California, San Diego, La Jolla, CA 92093); Brooks, L. *Nucleic Acids Res* 4(12): 4279-4289; 1977.

The question of whether proteins dissociate from chromatin during transcription in vitro was investigated using the viral transcription complex (VTC), a small fraction ( $< 1\%$ ) of the simian virus 40 (SV40) chromatin isolated from infected monkey cell cultures and containing active RNA polymerase that had initiated transcription in vivo.  $^3\text{H}$ -RNA was synthesized by the VTC under conditions such that over half the label was in transcripts that were longer than half the length of the SV40 genome. Almost all of the  $^3\text{H}$ -RNA remained associated with the SV40 chromatin, causing an increase in sedimentation rate from 55S to 78S. The density of the VTC-RNA complex indicated that  $< 5\%$  of the original protein dissociated from the SV40 DNA that served as a template for transcription. It is concluded that extensive transcription of SV40 chromatin in vitro by endogenous RNA polymerase II does not result in the release of protein from the viral DNA. (28 refs.)

- 78-0374 **Fine Structure of SV40 DNA-Chromatin Protein Complexes (Meeting Abstract).** (Eng) Hida, H. (Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama, 700, Japan); Omura, S.; Tanabe, N.; Hida, T. *J Electron Microsc (Tokyo)* 26(3): 226; 1977. (no refs.)

- 78-0375 **Ribosomal Proteins in Normal Simian Cells, SV40-transformed Simian Cells, and Simian Cells Infected with SV40, Adenovirus 5, and Vesicular Stomatitis Virus.** (Eng) Bosselman, R. A. (Dept. Microbiology, Univ. Massachusetts, Amherst, MA 01003); Price, J. A.; Burns, A. L.; Kaulenas, M. S.; Norkin, L. C. *Intervirology* 11(1): 8-15; 1978.

The composition of ribosome-associated proteins isolated from the T-22 line of simian virus 40 (SV40)-transformed green monkey kidney (GMK) cells, normal CV-1 GMK cells, and CV-1 infected with vesicular stomatitis virus (vsv), hu-

man adenovirus 5 (Ad5) and SV40 was analyzed by two-dimensional polyacrylamide gel electrophoresis, proteins from uninfected T-22 and CV-1 cells were first compared. The T-22 monosomes contained a protein component that was not detectable in CV-1 monosomes or the polysome fraction of CV-1 monosomes or the polysome fraction of either type. Infection of CV-1 cells with SV40 did not result in any qualitative change in the protein pattern of either the monosomal or polysomal fractions. Polysomal profiles from T-22, CV-1, and SV40-infected CV-1 cells were similar. Infection of CV-1 cells with Ad5 or VSV reduced the relative number of large polysomes, but there were no changes in monosome or polysome patterns. These results suggest that the SV40-induced enhancement of human adenovirus replication and the Ad5- and VSV-induced shutdown of cellular protein synthesis are not explained by changes in the protein composition of ribosomes. (22 refs.)

- 78-0376 **Distribution of a Major Surface-associated Glycoprotein, Fibronectin, in Cultures of Adherent Cells.** (Eng) Mosher, D. F. (Dept. Virology, Univ. Helsinki, Helsinki, Finland SF-00290); Saksela, O.; Keski-Oja, J.; Vaheri, A. *J Supramol Struct* 6(4): 551-557; 1977.

The distribution of fibronectin, a major surface-associated glycoprotein, was studied in a variety of adherent cells. Newly established adherent cell strains from human embryonic skin, heart, chest wall, lung, kidney, and liver were compared to one another and to established strains from adult skin and embryonic lung and lines of rhabdomyosarcoma cells and simian virus 40 (SV40)-transformed embryonic lung cells. All cultures had fibronectin in both the media and the cell layers. The newly established strains produced and secreted more fibronectin than the older established strains, which in turn secreted more fibronectin into the medium than transformed lines. Cell-surface fibronectin, visualized by immunofluorescence, was in dense fibrillar (lung cultures), discrete fibrillar (cultures from skin, liver, and chest wall), or punctate (some kidney cultures) structures. The subunit sizes of cell-surface fibronectin and fibronectin soluble in medium appeared identical in sodium dodecyl sulfate-polyacrylamide gels. Cell-surface fibronectin was missing from the surfaces of the rhabdomyosarcoma and SV40-transformed embryonic lung cells and only intracellular fibronectin was seen. The polymorphism of cell-surface fibronectin may be explained by chemical differences among the fibronectins synthesized by different cell strains or by factors in the cell layer which influence fibronectin binding and aggregation. Analysis of the factors that influence the binding of fibronectin to normal cells may lead to an understanding of why most transformed cells, which do not secrete or shed fibronectin, fail to bind it to their surfaces. (14 refs.)

- 78-0377 **Simian Virus 40-specific Proteins in the Membranes of Simian Virus 40-transformed Hamster**



and Mouse Cells. (Eng) Schmidt-Ullrich, R. (Tufts-New England Medical Center, Therapeutic Radiology Dept., Radiobiology Div., 171 Harrison Ave., Boston, MA 02111); Thompson, W. S.; Lin, P. S.; Wallach, D. F. *Proc Natl Acad Sci USA* 74(11): 5069-5072; 1977.

Simian virus 40 (SV40)-specific proteins in the membranes of transformed GD248 hamster lymphocytes, SV40 T-antigen-positive T19 cells, and transformed BALB/c SV3T3 mouse fibroblasts were investigated. Two classes of antigenic virus-specific protein that were not detectable in normal lymphocyte populations or embryonic hamster cells were found in the three lines. Their isoelectric points (pI) were at pH 4.5 and 4.7. the mol wts of the pI 4.5 and pI 4.7 components were approx 58,000 and 90,000-110,000 daltons, respectively. The pI 4.7 component reacted with U but not T antigen, identifying it with the SV40 U antigen; the pI 4.5 component was identified with the SV40 surface (transplantation) antigen. (15 refs.)

**78-0378 Virus Shedding by SV40-transformed Human Cells.** (Eng) Lomax, C. A. (3 Bailey Ford, Westhaughton Bolton BL5 3H4, England); Thirion, J. P.; Bourgaux-Ramoisy, D. *Intervirology* 9(1): 39-47; 1978.

Untransformed human skin cultures from healthy donors were transformed by simian virus 40 (SV40), and the shedding of virus was examined. Line ML was infected with wild-type SV40 and lines M5 and M2 were infected with the SV40 temperature-sensitive mutant tsA30. Virus shedding occurred in 12/14 M5 cultures, 2/4 M2 cultures, and 2/3 ML cultures. In one wild type-transformed line, T227, the yield of virus decreased with each passage, but the yield of another wild-type transformed line, T233, was not diminished through eight passages. Experiments with anti-SV40 antiserum indicated that the persistence of virus shedding did not require the spread of virus through the medium. Further analysis of the shedding cultures indicated that 1% of the cells at any passage were actively shedding. At early passages of line T227, there was a 15- to 20-fold greater yield of virus at 39 C compared to 33 C; however, shedding ceased beyond passage 6. Cells transformed by tsA30 produced approx 30 times more virus at 33 C than at 39 C. When GM30 xeroderma pigmentosum cells were infected with wild-type SV40, cell lines from 3/5 colonies were found to shed virus. Thus, the enzymes involved in the excision and repair of UV-induced damage to DNA are probably not involved in virus shedding. (13 refs.)

**78-0379 Transformation of Human Cells by Temperature-sensitive Mutants of Simian Virus 40.** (Eng) Lomax, C. A. (3 Bailey Ford, Westhaughton Bolton BL5 3H4, England); Bradley, E.; Weber, J.; Bourgaux, P. *Intervirology* 9(1): 28-38; 1978.

The transformation of human skin cells from healthy donors by 0.2 ml of wild-type simian virus 40 (SV40): ( $2 \times 10^6$  plaque-forming units (PFU)/ml) or the SV40 temperature-sensitive mutants tsA30 ( $1.2 \times 10^7$  PFU/ml) or tsB1 ( $7 \times 10^7$  PFU/ml) was investigated. The frequency of transformation by wild-type virus at both 39 and 33 C was close to unity. The transformation frequency of tsA30 was three to five times higher at 39 C than at 33 C, and that of tsB1 was increased by a factor of 2.6 at the restrictive temperature. There was an inverse relationship between transformation frequency by tsA30 and the time of incubation at 33C preceding that at 39 C, with the transformation frequency being reduced 25% by 1-2 days incubation at 33 C. Transformation by wild-type virus was insensitive to temperature shifts. There was little difference in viral yield during productive infection by wild-type virus at 33 and 39 C. However, there was a 96-fold reduction in yield for tsA30 at the restrictive temperature. At 33, 39, and 40 C cell density was low for untransformed cells, but it was three to five fold greater for wild-type-transformed cells. Cells transformed by tsA30 had three- to four-fold greater densities than untransformed cells at 33 and 39. At 40 C, they however, failed to grow to a density higher than that of untransformed cells. Increasing the temperature to 40.5 C caused tsA30-transformed cells to lose T antigen and to lose their ability to grow to high density; this effect was not seen with wild-type-transformed cells. (19 refs.)

**78-0380 Incidence, Latency, and Morphologic Types of Neoplasms Induced by Simian Virus 40 Inoculated Intravenously into Hamsters of Three Inbred Strains and One Outbred Stock.** (Eng) Diamandopoulos, G. T. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115). *J Natl Cancer Inst* 60(2): 445-449; 1978.

The incidence, latency, and morphologic types of neoplasms induced in inbred hamster strains LSH/SsLak, LHC/Lak, and MHA/SsLak, inoculated iv at 3 wk of age with  $10^5$  of the infective TCD50 simian virus 40 (SV40), were determined and compared with those of outbred LVG/Lak animals. Although tumor incidence and latency were approx the same in the three inbred strains, outbred hamsters exhibited almost complete resistance to tumor induction under identical experimental conditions. The morphologic types of neoplasms, (lymphocytic leukemia, reticulum cell sarcoma, osteogenic sarcoma, and anaplastic sarcoma), induced in inbred hamsters were similar to those induced in outbred hamsters inoculated iv with  $10^{5.5}$  of the SV40 infective TCD50. The lymphocytic leukemias that developed in the two LSH/SsLak inbred hamsters were established as tumor transplants in vivo and as permanent cell lines in vitro. (24 refs.)

**78-0381 Enhanced SV40 Virus Replication in Fully Permissive Monkey Kidney Cells Pretreated with**



**5-Iodo-2'-deoxyuridine (IdUrd).** (Eng) Suarez, H. G. (Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800, Villejuif, France); Lavialle, C.; Stevenet, J.; Estrade, S.; Morris, A. G.; Cassingena, R. *J Gen Virol* 37(3): 569-584; 1977.

The effect of pretreatment of CV<sub>1</sub>Cl<sub>1</sub> monkey kidney cells with 5-iodo-2'-deoxyuridine (IdUrd) before infection with a large plaque strain of simian virus 40 (SV40) was investigated. Following treatment of cells with 100 µg/ml IdUrd, the cells were infected with 0.1 multiplicities of infection or 1 plaque forming unit/cells. Early after infection, the total yield of virus in the pretreated cultures was significantly higher than controls. With a low multiplicity of infection and low temperature, a 10- to 50-fold enhancement of virus yield was noted. Different concentrations of the drug and shorter treatment periods with the fixed dose were less effective in stimulating virus production. Slowing of growth rate at 33°C resulted in a prolonged enhancement of virus yield, but an increase in virus production was not detectable when the cells were infected at high multiplicities. Pretreatment also enhanced SV40 DNA replication and the number of V-antigen and virus-synthesizing cells. The potentiating effect was not observed when the pretreated cells were infected with SV40 DNA. T-antigen synthesis was increased even in the presence of 5 µg/ml cytosine arabinoside. Although IdUrd inhibited cellular DNA synthesis, the incorporation of uridine and leucine into RNA and proteins was unaffected. Late virus functions were preferentially expressed in the absence of cellular DNA synthesis. These findings are discussed. (24 refs.)

**78-0382 Anchorage Independence and Predictable Crisis in SV40-transformed Cells (Meeting Abstract).** (Eng) Ruben, R. L. (Dept. Anatomy, Univ. Illinois Medical Center, Chicago, IL); Rafferty, K. A. *Anat Rec* 189(3): 551; 1977. (no refs.)

**78-0383 Purification by Affinity Chromatography and Preliminary Characterization of Ornithine Decarboxylase from Simian Virus 40-transformed 3T3 Mouse Fibroblasts.** (Eng) Boucek, R. J. (Dept. Pediatrics, Vanderbilt Univ. Sch. Medicine, Nashville, TN 37232); Lembach, K. J. *Arch Biochem Biophys* 184(2): 408-415; 1977.

Ornithine decarboxylase (OD) was purified from simian virus 40-transformed 3T3 mouse fibroblasts by a procedure utilizing affinity chromatography as the principal step. Selective elution of the enzyme from a pyridoxamine 5'-phosphate-agarose affinity matrix with pyridoxal 5'-phosphate effected a single-step purification of approx 500-fold, with a significantly higher overall recovery of activity (30%-45%) than that achieved with previous procedures. In the presence of optimal protein concentrations, the enzyme from transformed fibroblasts exhibited a significantly higher specific activity than the decarboxylase purified from liver. The ap-

parent affinities of the fibroblast enzyme for substrate and cofactor were similar to those reported for the decarboxylases purified from other tissues. With the use of sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the subunit mol wt of the purified OC was approx 55,000, while the apparent mol wt of the active enzyme in vitro, as determined by gel filtration, was approx 110,000. (24 refs.)

**78-0384 Lysosomal Glycosidases in Normal and SV40-Transformed Hamster Fibroblasts as a Function of the Cell Cycle. Effect of Cycloheximide.** (Fre) Maziere, J. C. (Service de Chimie Biologique, C.H.U. Saint-Antoine, 27, rue Chaligny, 75571 Paris Cedex 12, France); Maziere, C.; Polonovski, J. *Biol Cellulaire* 30(1): 1-4; 1977.

The activity of N-acetyl-beta-glucosaminidase and beta-galactosidase in various phases of the cell cycle of simian virus 40-transformed (EHSVi) and untransformed (EHB) hamster fibroblasts was investigated. The cells were cultured in enriched Eagle's Minimum Essential Medium with 2.5%-15% calf serum. In all phases of the cell cycle, the glycosidase activity was approx 50% higher in the transformed cells. In both EHB and EHSVi cells, enzyme activity increased as the cells moved from the exponential phase to the stationary phase. Enzyme activity also increased when the concentration of calf serum was decreased; however, EHSVi cells appeared less sensitive to the medium alteration. Cycloheximide ( $3.6 \times 10^{-6}$  M) was added to the cultures 3 days after they were seeded, and enzyme activity was measured on the 2 succeeding days. The cycloheximide-induced decrease in enzyme activity was greater in the EHB cells. Although both N-acetyl-beta-glucosaminidase and beta-galactosidase activities were equally sensitive to the presence of cycloheximide in the EHB cells, beta-galactosidase activity did not diminish as much as that of N-acetyl-beta-glucosaminidase in response to the agent in the EHSVi cells. It is concluded that virus-transformed cells are less sensitive to culture conditions. (16 refs.)

**78-0385 Heterokaryons between Chick Erythrocytes and SV40 Induced H-50 Tumour Cells (Meeting Abstract).** (Eng) Szucs, G. (Public Health Station, Pecs, Hungary); Kellermayer, M. *Acta Microbiol Acad Sci Hung* 24(1): 76; 1977. (no refs.)

**78-0386 Lymphocyte Stimulation by Urine-derived Human Polyoma Virus (BK): Brief Report.** (Eng) Lecatsas, G. (Dept. Microbiology, Inst. Pathology, Univ. Pretoria, P. O. Box 2034, Pretoria 0001, S. Africa); Blignaut, E.; Schoub, B. D. *Arch Virol* 55(1/2): 165-167; 1977.



The stimulation of human lymphocytes in culture by urine-derived BK polyoma virus, as measured by  $^3\text{H}$ -thymidine incorporation, is reported. The virus was obtained from the urine of a renal transplant patient, and it was indistinguishable from BK virus by hemagglutination inhibition. The possibility that human polyoma viruses may result in inefficient antibody synthesis and/or reduced cell-mediated immunity is discussed. (11 refs.)

- 78-0387 In Vitro Polyoma DNA Synthesis: Asymmetry of Short DNA Chains.** (Eng) Hunter, T. (Tumor Virology Lab., Salk Inst., P.O. Box 1809, San Diego, CA 92112); Francke, B.; Bachelier, L. *Cell* 12(4): 1021-1028; 1977.

The replication of polyoma DNA was studied by annealing the separated strands of polyoma DNA Hpa II restriction fragments 1 and 2 to purified short DNA chains isolated from in vitro pulse-labeled replicating polyoma DNA. For each growing fork of polyoma replicative intermediate, the DNA strand that had to grow discontinuously was represented about four times as often in the population of short DNA chains as the strand able to replicate continuously. The absolute concentration of short DNA chains in the two growing forks was approx the same. The av sizes of the short DNA chains from the continuous and discontinuous strand were similar. It is concluded that polyoma DNA replication in vitro proceeds predominantly by a semidiscontinuous mechanism. It is suggested that in vivo replication also proceeds through a semidiscontinuous mechanism. (37 refs.)

- 78-0388 Synthesis and Transport of Polyoma Virus-Specific RNA in Productively-Infected Cells (Meeting Abstract).** (Eng) Acheson, N. H. (Swiss Inst. Experimental Cancer Res., ch. de Boveresses, 1066 Epalinges, Lausanne, Switzerland). *Biol Cellulaire* 29(2/3): 48a; 1977. (no refs.)

- 78-0389 Modulation of the Nucleoside Transport System of Mammalian Cells by Polyoma Virus and Photoaffinity Probes (Meeting Abstract).** (Eng) Scala, A. M. (Univ. Rochester, Rochester, NY). *Diss Abstr Int [B]* 38(6): 2546-B; 1977. (no refs.)

- 78-0390 The Structure of Replicating Adenovirus 2 DNA Molecules.** (Eng) Lechner, R. L. (Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205); Kelly, T. J. *Cell* 12(4): 1007-1020; 1977.

Replicating adenovirus 2 (Ad2) DNA molecules were studied by electron microscopy to determine their structure and replicative mechanism. Ad2-infected KB cells were exposed to a 2.5-min pulse of  $^3\text{H}$ -thymidine at 19 hr after infection. The labeled DNA molecules were separated from cell DNA and mature Ad2 DNA by sucrose gradient sedimentation and CsCl equilibrium centrifugation under conditions designed to minimize branch migration and hybridization of single strands. Electron microscopy of fractions containing radioactivity revealed two types of replicating molecules: Ad2-length duplex DNA molecules with one or more single-stranded branches and Ad2-length linear DNA molecules with a single-stranded region extending a variable distance from one end. The data indicate that replication is initiated at or near an end of the Ad2 duplex and that initiations at the right and left ends are approx equal in frequency. Following initiation, a daughter strand is synthesized in the 5' to 3' direction, displacing the parental strand with the same polarity. Synthesis of the complementary daughter strand is initiated at or near the 3' end of the displayed parental strand, and it also proceeds in the 5' to 3' direction. (45 refs.)

- 78-0391 Histone Synthesis Is Not Coupled to the Replication of Adenovirus DNA.** (Eng) Tallman, G. (Dept. Biochemistry, Kansas State Univ., Manhattan, KS 66506); Akers, J. E.; Burlingham, B. T.; Reeck, G. R. *Biochem Biophys Res Commun* 79(3): 815-822; 1977.

Labeled deoxythymidine and lysine were incorporated into KB cells infected with 50-100 plaque forming units of purified adenovirus type 2 to study histone synthesis during viral DNA synthesis. Both DNA and histone synthesis decreased during the initial 12 hr of infection. However, as viral DNA synthesis increased, histone synthesis continued to decrease. The incorporation of lysine into the core histones was approx 50 x lower at 18 hr than it was 2 hr after infection. This lack of histone synthesis during viral DNA replication does not exclude the possibility that histones might form complexes with adenovirus DNA. (24 refs.)

- 78-0392 Sizing and Mapping of Early Adenovirus mRNAs by Gel Electrophoresis of S1 Endonuclease-digested Hybrids.** (Eng) Berk, A. J. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Sharp, P. A. *Cell* 12(3): 721-732; 1977.

By hybridizing unlabeled RNA to labeled DNA and treating the hybrid with endonuclease S1, the early cytoplasmic colinear transcripts produced in adenovirus 2 (Ad2)-infected HeLa cells were mapped. All early transcripts were clustered in four regions of the viral DNA. At least five early stable cytoplasmic colinear transcripts were transcribed from left to right in the region of the viral genome coding functions necessary for transformation of mammalian cells. Transcripts of 650, 350, and 1,750 nucleotides map from 1.7 to 3.6, 3.6



4.6, and 4.7 to 9.5 units, respectively; two 450-nucleotide transcripts mapped between 3.0 and 11.0 units. Two overlapping transcripts having the same 3' terminus were transcribed on the left from 66.2 to 61.6 and 66.5 to 61.6 units, respectively. Seven other early transcripts were also positioned. It is suggested that the region from 1.7 to 3.6 units may code for the 15 500 dalton protein that has been suggested to harbor the transforming activity. (39 refs.)

**78-0393 The Gene and Messenger RNA for Adenovirus Polypeptide IX.** (Eng) Pettersson, U. (Dept. Microbiology, Biomedical Center, Uppsala Univ., Uppsala, Sweden); Matthews, M. B. *Cell* 12(3): 741-750; 1977.

A small RNA species was purified from adenovirus-2-infected HeLa cells by a novel screening technique, and its properties were examined. This RNA fragment, which hybridized to fragment Sma I-E, sedimented at 9S and was approximately 100 nucleotides long. Affinity chromatography suggested that the 9S molecule had a messenger function. Hybridization with Bam HI fragments revealed that the RNA was contained between map coordinates 9.4 and 11.1 on the r strand of the DNA, a region corresponding to about 590 base pairs. Polypeptide IX, a late protein with a mol wt of 12,000 daltons, was transcribed from the molecule in a cell-free translation system. Thus, the gene for a late protein is located in a region of the genome that is transcribed early in infection. (5 refs.)

**78-0394 The Initiation Sites for RNA Transcription in Ad2 DNA.** (Eng) Evans, R. M. (Rockefeller Univ. New York, NY 10021); Fraser, N.; Ziff, E.; Weber, J.; Olson, M.; Darnell, J. E. *Cell* 12(3): 733-739; 1977.

RNA pulse-labeled in vivo and in vitro was used to map the initiation sites for RNA transcription in adenovirus type 2 (Ad2) DNA. Six restriction fragments containing sites for RNA initiation were found. Four initiation sites early in infection were identified as containing transcription units 0-4, 83, 59-76, and 90-100. All four regions showed RNA transcripts that began in one fragment and extended into a neighboring fragment. The results show that the early messenger RNA's (mRNA's) previously mapped within these regions derived from four independent transcription units. The major late RNA initiation site is the origin of a giant nuclear transcript extending from approx 16.3 map units to approx 100 map units at the end of the genome. This transcription unit encompasses at least four or five mRNA sites; processing of this long transcript appears necessary to generate the late mRNA. (23 refs.)

**78-0395 Transcription of Specific Adenovirus Genes in Isolated Nuclei by Exogenous RNA Polymerase.**

(Eng) Jaehning, J. A. (Dept. Biological Chemistry, Div. Biology and Biomedical Sciences, Washington Univ., St. Louis, MO 63110); Roeder, R. G. *J Biol Chem* 252(23): 8753-8761; 1977.

Previous studies showed that the endogenous RNA polymerase III in adenovirus-2 (Ad2)-infected KB cells mediated the synthesis of several low-mol-wt virus-coded RNA's, the most prominent of which was 5.5S RNA. In the present study, 5.5S RNA synthesis in the nuclei of infected KB cells was stimulated three- to fivefold by exogenous KB RNA polymerase IIIA and IIIB isolated from uninfected or virus-infected KB cells. Similar results were obtained with class III RNA polymerases from mouse plasmacytoma cells and from *Xenopus laevis* oocytes. The RNA polymerase III activity in isolated nuclei was inactivated irreversibly by low concentrations of N-ethylmaleimide. All class III RNA polymerases that stimulated viral 5.5S RNA synthesis in untreated nuclei from virus-infected cells also enhanced the 5.5S RNA synthesis in N-ethylmaleimide-treated nuclei. However, the degree of stimulation above the residual endogenous RNA polymerase level was much higher in N-ethylmaleimide-treated nuclei (up to thirtyfold). In contrast, neither RNA polymerase II from adenovirus-infected cells nor *Escherichia coli* RNA polymerase selectively enhanced the transcription of the viral 5.5S genes in isolated nuclei, although total RNA synthesis levels increased in each case. (36 refs.)

**78-0396 Human Cell Cultures Infected by Tumor-inducing and Non-tumor-inducing Viruses, an Electron Microscopic Study.** (Eng) Sun, C. N. (EM Lab., Veterans Admin. Hosp., 300 E. Roosevelt Road, Little Rock, AR 72206); Hsu, D.; Pinkerton, H. *Exp Pathol (Jena)* 14(1/2): 9-15; 1977.

The effect of adenovirus types 2 or 12 (Ad2 or Ad12) infection on KB, WI, or MAF human fibroblasts was investigated. With the exception of Ad12-WI, many intranuclear viral particles were detected. None of the cells of second passages (Ad2-WI-WI, Ad12-WI-WI, Ad2-MAF-MAF, or Ad12-MAF-MAF) had any virus production, and there were no dense osmophilic materials or nuclear inclusions. However, when infected WI and MAF cells were used to expose KB cells, significant viral yields were obtained. These findings indicate that although Ad2 and Ad12 cannot be transmitted serially, the infected cells might still carry virus-specific antigens even though no visible virions were observed. It is suggested that a lack of homology between the Ad12 viral DNA and the DNA of WI cells prevents the production of viral progeny in WI cells. (5 refs.)

**78-0397 Purification and Characterization of Adenovirus Type 12 Tumor Antigen (Meeting Abstract).** (Eng) Biron, K. K. (Rutgers Univ. State Univ. New Jersey, New Brunswick, NJ). *Diss Abstr Int [B]* 38(5): 2040B-2041B; 1977. (no refs.)



- 78-0398 An Altered Subunit Configuration Associated with the Actively Transcribed DNA of Integrated Adenovirus Genes.** (Eng) Flint, S. J. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ 08540); Weintraub, H. M. *Cell* 12(3): 783-794; 1977.

The sensitivity to DNase I or viral DNA sequences integrated into the genome of two adenovirus type 5 (Ad5)-transformed hamster cell lines (HT14A and HT14B) was investigated. The HT14A line contained 2.4 copies of the left-hand 35% of the Ad5 genome per diploid quantity of cell DNA. All integrated sequences coding for messenger RNA (mRNA) were sensitive to DNase I, as were some additional sequences, equivalent to three to four nucleosomes, to the 5' side of the stable mRNA transcript. Thus, there is a correspondence to within three to four nucleotides between the structure of the active transcription unit and the stable mRNA sequences encoded by it. HT14B cells contained 5.5 copies of the left-hand 40% of the Ad5 genome per diploid quantity of cell DNA. Only half the sequences complementary to viral mRNA were preferentially sensitive to DNase I. The majority of the integrated viral DNA sequences not expressed as mRNA were resistant to the enzyme in both lines. These findings suggest that with HT14B, only half the integrated sequences are in a chromatin configuration permitting transcription. Reasons for the observed behavior are discussed. (27 refs.)

- 78-0399 Replication of Herpes Simplex Virus in Human Peripheral T Lymphocytes.** (Eng) Kirchner, H. (Inst. Virus Res., German Cancer Res. Centre, Heidelberg, W. Germany); Kleinicke, C.; Northoff, H. *J Gen Virol* 37(3): 647-649; 1977.

Human T and B lymphocytes were separated into homogeneous groups and tested for their ability to replicate herpes simplex virus-1 (HSV) (WAL) in vitro. The cells were stimulated with optimal doses of mitogens prior to infection. Only T cells activated by phytohemagglutinin, concanavalin A or pokeweed mitogen showed virus replication. It was not possible to determine whether human B cells activated by a B cell mitogen could also replicate HSV (WAL). Furthermore, it was not possible to determine whether activated B cells in the absence of T cells could replicate the virus. These findings are compared to those in mice where activated B cells can replicate HSV. (13 refs.)

- 78-0400 Cell-free Synthesis of Herpes Simplex Virus DNA: Conditions for Optimal Synthesis.** (Eng) Francke, B. (Tumor Virology Lab., Salk Inst. Biological Studies, San Diego, CA 92112). *Biochemistry* 16(26): 5655-5664; 1977.

The optimal conditions for two cell-free DNA synthesis systems derived from herpes simplex virus type 1 (HSV-1)-infected BHK cells were examined: (1) an unfractionated

hypotonic lysate and (2) purified nuclei. The former contained altered deoxynucleotide triphosphate pools at 15 hr postinfection, compared with uninfected lysates. The thymidine triphosphate (TTP) pool was max at 12 hr postinfection at 31 C. This pool was utilized in vitro for the synthesis of viral and cellular DNA in the lysate, and it was reduced to 1.5  $\mu$ M in purified nuclei. A concentration of 10  $\mu$ M deoxy-ATP and TTP and 50  $\mu$ M cyclic triphosphate and deoxy-guanosine triphosphate were required for max synthesis in purified nuclei. The initial rate of synthesis in purified nuclei was independent of added ATP or the other three ribonucleoside triphosphates. Concentrations up to 0.5 mM ribonucleoside triphosphate stabilized the in vitro product against nucleolytic degradation. Similar effects were observed with TTP, creatine phosphate, and inorganic pyrophosphate. Chloride was inhibitory above 40 mM in the nuclear system and at all concentrations in the lysate. The  $Mg^{+2}$  optimum corresponded to that of uninfected systems, and the concentration for cellular DNA synthesis was lower than that for viral DNA synthesis. Purified nuclei had a pH optimum between pH 7 and 8; the lysate system had optima at pH 6 and 9. Addition of cytosol from uninfected cells to purified nuclei was slightly inhibitory, but addition of cytosol from infected cells stimulated initially and resulted in degradation of in vivo prelabeled and in vitro labeled viral DNA at later times. (27 refs.)

- 78-0401 Cell-Free Synthesis of Herpes Simplex Virus DNA: Structure of the In Vitro Product and Nucleolytic Degradation.** (Eng) Francke, B. (Tumor Virology Lab., Salk Inst. Biological Studies, San Diego, CA 92112). *Biochemistry* 16(26): 5664-5670; 1977.

A study was made of the size of the viral DNA products synthesized in cell-free DNA synthesis systems from herpes simplex virus type 1 (HSV-1)-infected baby hamster kidney (BHK) cells under conditions that minimize degradation or favor certain nucleolytic activities. Viral DNA from lysates of nuclei of HSV-infected cells incubated under optimal conditions remained stable against nucleolytic degradation to acid-soluble material. The size of this viral DNA ranged from 20S to 50S, but this range probably does not reflect the actual size of the viral DNA in the cell. When the lysate was denatured with alkali, the viral DNA sedimented between 1s and 40s. In the absence of additional divalent cations other than  $Mg^{2+}$ , the lysate system had almost no endogenous nucleolytic activity. However, endonucleases could be stimulated by the addition of  $Ca^{2+}$ . Degradation of viral DNA in the concentrated lysate may be impeded by an inhibitor of nucleases and/or a DNA protecting agent, since diluted lysate demonstrated endonucleolytic activity. Isolated nuclei washed with 60 mM KCL on longer had exonuclease activity but they did retain endonuclease activity, resulting in a DNA product of 11S.  $Mg^{2+}$  was required for this degradation. All the in vitro nucleolytic events were specific for viral DNA and cellular DNA was not affected. (16 refs.)



**78-0402 Regulation of Translation of DNA Viruses: Inhibition of Herpes Simplex Virus Type 1 (HSV1) and Simian Virus 40 (SV40) Protein Synthesis by poly(I):poly(C)-Induced Interference (Meeting Abstract).** (Eng) Lipp, M. (Institut für Virologie, Hermann-Herder-Str. 11, D-7800 Freiburg i.Br., W. Germany); Manner, H.; Brandner, G. *Hoppe Seylers Z Physiol Chem* 358(10): 1241; 1977. (no refs.)

**78-0403 Incidence and Distribution of Herpes Simplex Virus Types 1 and 2 from Genital Lesions in College Women.** (Eng) Kalinyak, J. E. (Dept. Microbiology and Cell Biology, Pennsylvania State Univ., University Park, PA 16802); Fleagle, G.; Docherty, J. J. *J Med Virol* 1(3): 175-181; 1977.

Herpetic genital infections were diagnosed in 57/9,772 college women treated at a student health center's gynecology unit over a 9-mo period. Herpes simplex virus (HSV) was isolated from 30/57 patients, yielding an incidence rate of 0.31%. Of the isolates, 37% were classified as HSV type 1 and 63% as HSV type 2 on the bases of heat stability of the viral thymidine kinase and virus plaque diameter in chick embryo cells. The possible etiologic role of both HSV types in cervical cancer is discussed briefly. (17 refs.)

**78-0404 Measurement of Antibodies to Herpesvirus Types 1 and 2 in Human Sera by Microradioimmunoassay.** (Eng) Jankowski, M. A. (Natl. Inst. Hygiene, 0791 Warsaw, Poland); Petersen, E. E.; Bocker, J. F. *Acta Virol (Praha)* 21(5): 405-411; 1977.

The binding of  $^{125}\text{I}$ -labeled antihuman antibodies against the rG Fc fragment to unlabeled antiviral immunoglobulins on the surface of infected cells was used to quantitate antibodies against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in sera from cervical carcinoma patients. The microradioimmunoassay technique (micro-RIA) was 5-10 times more sensitive than the microneutralization test. Antibody titers determined by micro-RIA correlated with neutralizing antibody titers to both HSV-1 and HSV-2. The relative antibody titers to HSV-1 and HSV-2, as determined by micro-RIA, could be used to distinguish persons previously infected with HSV-2 by means of II/I neutralization indices. (16 refs.)

**78-0405 Studies on Tumors Produced by Cells Transformed with Herpes Simplex Virus Type 2.** (Eng) Takeichi, S. (Second Dept. Pathology, Sch. Medicine, Tokushima Univ., Kuramoto-cho 3-chome, Tokushima 770, Japan); Kimura, S. *Gann* 68(5): 653-661; 1977.

The biological, histological, and ultrastructural characteristics of tumors produced in weanling hamsters by herpes simplex virus type 2 (HSV-2)-transformed hamster embryo fibroblasts and by cultured cells (primary and secondary lines  $T_1$  and  $T_2$ ) derived from these tumors are reported. The transformed cells (line 155-4) produced tumors in weanling hamsters, but only at a high passage level (114th) in vitro and after a 24-hr latent period; the incidence of metastasis was 20%. The tumor cell lines (155-4 $T_1$  and 155-4 $T_2$ ) produced tumors after a shorter latent period (8 days) and with a much higher incidence of metastasis (89% and 100%, respectively). Thus, the malignancy of the transformants increased with passages in vitro and in vivo. Lines 155-4 $T_1$  and U-15 $T_1$  produced fibrosarcomas, line U-26 $T_1$  lesions resembling human malignant fibrous histiocytomas (MFH). This variation in histology could be due to a multitransforming potential of the virus stock or to a variety in the target cells. Ultrastructurally, the fibrosarcomas consisted of fibroblastlike cells with extracellular collagen fibers. The MFH-like lesions consisted of undifferentiated cells, multinuclear giant cells, histiocytelike cells, and fibroblastlike cells. Several kinds of nuclear body-type inclusions were found in the cells of tumors produced by all three lines (155-4 $T_1$ , U-15 $T_1$ , and U-26 $T_1$ ). Those found in the U-26 $T_1$  tumor cells were very similar to the inclusions of human MFH cells. There were herpesviruslike particles in a few nuclei of the U-26 $T_1$  undifferentiated tumor cells. They had capsidlike structures enclosing electron-dense cores and a diameter of 120-140 nanometers. (19 refs.)

**78-0406 Induction of Latent Herpes Simplex Virus Type 2 Infection in Human Cervical Epithelial Cells In Vitro.** (Eng) Vesterinen, E. (Lab. Pathology and Cytology, Depts. Obstetrics and Gynecology, Univ. Central Hosp., Haartmanink 2, Helsinki 29, Finland); Leinikki, P.; Saksela, E. *Acta Pathol Microbiol Scand [B]* 85(5): 289-295; 1977.

Adenine arabinoside (ara-A) was used to induce latent herpes simplex virus type 2 (HSV-2) infections in cultured human ecto- and endocervical epithelial cells. The cell cultures were initiated from patients undergoing hysterectomy for benign gynecological conditions. The cultures were inoculated with  $1 \times 10^3$  to  $1 \times 10^5$  TCID<sub>50</sub> of HSV-2 per coverslip. If the virus input dose was not  $> 1 \times 10^3$  TCID<sub>50</sub>, 20  $\mu\text{g}/\text{ml}$  ara-A was capable of blocking productive infection without disturbing cell proliferation. When ara-A was withdrawn after  $\leq 72$  hr of culture, activation was observed with both endo- and ectocervical cells. Except for two ectocervical cultures, no morphological signs of HSV-2 infection were apparent when blocking was continued for longer periods. The HSV-2-induced cytopathetic effect resembled that observed in untreated cultures. Fluorescent antibody studies detected virus-specific proteins in cells of infected explants blocked by ara-A, but productive infection was not observed. The fluorescence prevailed in the cytoplasm of blocked cells, whereas the fluorescence was present throughout unblocked cells. These findings indicate that human ecto- and endocervical cells are suitable targets for investigations of HSV-2 latency. (16 refs.)



**78-0407 Interactions Between Superinfecting Herpesviruses and Resident Type C RNA Virus Genomes in Mammalian Cells (Meeting Abstract).** (Eng) Reed, C. W. (Pennsylvania State Univ., PA). *Diss Abstr Int [B]* 38(5): 2050B; 1977. (no refs.)

**78-0408 Enzymology of Cells Infected with Herpes Virus.** (Rus) Petrovich, Yu. A. (Medical Stomatological Inst., Moscow, USSR); Terekhina, N. A. *Vopr Virusol* (6): 643-649; 1977.

Current data on the enzymology of cells infected with herpesvirus (HV) are reviewed. HV-infected cells show a marked elevation of various enzymes responsible for the de novo synthesis of specific viral nucleic acids and the degradation of host DNA. (71 refs.)

**78-0409 Scanning Electron Microscopy of the Surfaces of Hamster Embryo Cells Transformed by Herpes Simplex Virus.** (Eng) Glaser, R. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Mumaw, V.; Farugia, R. *Cancer Res* 37(12): 4420-4422; 1977.

The surfaces of normal hamster embryo fibroblast (HEF) cells were examined by scanning electron microscopy and compared with those of (1) cells derived from a primary tumor induced in hamsters following sc injection of herpes simplex virus type 1-transformed HEF cells (14-012-8-1) and (2) cells derived from a metastatic tumor to the lung induced by the same cells. The most obvious difference in surface characteristics was related to the morphology of the microvilli. In the few HEF cells that possessed microvilli, the distribution was uneven, and the lengths of the microvilli and the filopodia were variable. However, the surfaces of both tumor cell lines showed large numbers of microvilli that were evenly distributed over the surface of the cells, giving an almost hairy appearance. Long filopodia were occasionally observed on the surface of the primary tumor cell line and on the cell line derived from the metastatic tumor. Ruffles and blebs were occasionally observed of HEF cells and on the primary tumor cells, but they were not seen on the metastatic tumor cells. (12 refs.)

**78-0410 Effect of Herpesvirus Infection on the Mitotic Index and Cytogenetic Characteristics of Human Embryonic Lung (R) Cells (Meeting Abstract).** (Eng) Varadinova, T. L. (Faculty Biology, Univ. Sofia, Sofia, Bulgaria); Mincheva, A.; Andonov, P.; Bradvarova, I. *Acta Microbiol Acad Sci Hung* 24(1): 66; 1977. (no refs.)

**78-0411 Follow-up of Women with and without Herpesvirus-specific Antigens in their Cervical Cells (Meeting Abstract).** (Eng) Pacsa, S. (Inst. Microbiology and Dept. Obstetrics and Gynaecology, Univ. Medical Sch., Pecs, Hungary); Kummerlander, L.; Pejtsik, B.; Krommer, K. Pali, K. *Acta Microbiol Acad Sci Hung* 24(1): 56; 1977. (no refs.)

**78-0412 Chromosome Banding, Isoenzyme Studies and Determination of Epstein-Barr Virus DNA Content on Human Burkitt Lymphoma/Mouse Hybrids.** (Eng) Spira, J. (Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden); Povey, S.; Andersson-Anvret, M.; Wiener, F.; Klein, G. *Int J Cancer* 20(6): 849-853; 1977.

Four independently fused hybrid clones derived from a cross between the mouse mammary carcinoma line TA3Ha and the human Burkitt's lymphoma line Daudi were tested for Epstein-Barr virus (EBV)-determined nuclear antigen (EBNA), EBV DNA, and the presence of human chromosomes during serial propagation in vitro. EBV-DNA was detected by complementary RNA (cRNA)/DNA hybridization, EBNA by anticomplement fluorescence. The hybrids were also examined by horizontal starch-gel electrophoresis for the presence of human enzymes associated with particular chromosomes. With prolonged passage in culture, EBV-DNA and EBNA tended to disappear at a time when only a small number of human chromosomes were still present, but there was no correlation with the loss of any human chromosome. This suggests that the multiple viral genomes known to be carried by the EBV-positive Daudi line do not have one specifically integrated viral progenitor site but are propagated in random association with different chromosomes and/or exclusively in the free plasmid form. It is concluded that no specific human chromosome can be associated with the maintenance of the EBV genome in this hybrid combination. (15 refs.)

**78-0413 Biological Characterization of an Epstein-Barr Nuclear Antigen-positive American Burkitt's Tumor-derived Cell Line.** (Eng) Hillman, E. A. (Univ. Maryland Sch. Medicine, Dept. Pathology, 660 W. Redwood St. Baltimore, MD 21201); Charamella, L. J.; Temple, M. J. Elser, J. E. *Cancer Res* 37(12): 4546-4558; 1977.

Two distinct cultures (NAB I and II) derived from Burkitt's lymphoma cell line were characterized immunologically, morphologically, and cytogenetically. Both cultures were positive for Epstein-Barr nuclear antigen. NAB I culture were negative for virus capsid antigen and early antigen and were not affected by treatment with 5-iododeoxyuridine (IUdR). NAB II cultures were positive for virus capsid antigen and early antigen, a response that was increased with IUdR.



reatment. Both cultures were superinfected with virus prepared from P3HR-1 cells. Cell-free virus concentrates prepared from both cultures were inactive for transformation and infectivity. NAB I and NAB II cells were lymphoid, as determined by light and electron microscopy. NAB II cells showed morphological alterations characteristic of herpes infection. IUdR-treated cells from both cultures had the ultrastructural characteristics of cells infected with herpes virus but without virus particles. In addition, the induction of tubuloreticular structures within the endoplasmic reticulum was observed. Cytogenetic analysis of both cultures revealed rearranged chromosome 14 and several other chromosome aberrations, three of which may be useful in identifying NAB cultures. (54 refs.)

78-0414 **Detection of a Nuclear, EBNA-Type Antigen in Apparently EBNA-negative *Herpesvirus papio* (HVP)-transformed Lymphoid Lines by the Acid-fixed Binding Technique.** (Eng) Ohno, S. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden); Luka, J.; Falk, L.; Klein, G. *Int J Cancer* 20(6): 941-946; 1977.

A newly developed method to demonstrate Epstein-Barr nuclear antigen (EBNA) by extraction, concentration, and binding to acid-fixed Epstein-Barr virus (EBV)-negative cell nuclei was applied to *Herpesvirus papio* (HVP)-transformed baboon lymphoid cell lines. An EBNA-like antigen was readily detected in both producer and nonproducer lines, which were negative for EBNA by anticomplementary staining in situ. All anti-EBNA-positive sera gave an equally good reaction, whether they came from African Burkitt's lymphoma donors and were also positive for anti-early antigen (EA) antibodies or from healthy Swedish anti-EBNA-positive, anti-EA-negative donors. The involvement of viral capsid antigen (VCA) was ruled out by the isolation of antigen material from a nonproducer line that makes no VCA. The new antigen was designated HUPNA. Its detection by human anti-EBNA antibody suggests cross-reactivity, if not identity, between EBNA and HUPNA. Brilliant EBNA staining was induced in an HVP-carrying, nonproducer line negative for in situ anticomplementary staining but capable of yielding HUPNA by the nuclear binding technique. This suggests that lack of in situ stainability is a property associated with the baboon-derived virus, HVP, and not with the baboon lymphoid cell per se. (15 refs.)

78-0415 **Epstein-Barr Virus Induces Viral Nuclear Antigen in Nasopharyngeal Epithelial Cells (Letter to the Editor).** (Eng) Desgranges, C. (Unit Biological Carcinogenesis, International Agency Res. Cancer, 69372 Lyon, France); de-The, G. *Lancet* 2(8051): 1286-1287; 1977.

Cultures of cells from biopsy specimens taken opposite a nasopharyngeal carcinoma in four patients were infected with

a mixture of the transforming (M-81) and nontransforming (P3HR-1) strains of Epstein-Barr virus (EBV) and assayed for EBV nuclear antigen (EBNA). EBNA-positive epithelial cells were observed only in diethylaminoethyl-dextran-treated EBV-infected cells. These results indicate that EBNA expression can be induced in EBV-infected cells, but they do not prove that the cells have receptors for EBV. (12 refs.)

78-0416 **Comparative Studies on the Induction of Virus-associated Nuclear Antigen and Early Antigen by Lymphocyte-transforming (B95-8) and Nontransforming (P3HR-1) Strains of Epstein-Barr Virus.** (Eng) Menezes, J. (Ste-Justine Hosp., 3175 Ste-Catherine Road, Montreal H3T 1C5, Canada); Patel, P.; Dussault, H.; Bourkas, A. E. *Inter-virology* 9(2): 86-94; 1978.

The kinetics of the appearance of Epstein-Barr virus (EBV)-associated nuclear antigen (EBNA) and early antigen (EA) in different EBV-infected target cell systems was studied. In BJA-B cells, the lymphocyte-transforming EBV strain B95-8 induced EBNA 10 hr after infection, but the nontransforming EBV strain P3HR-1 induced EBNA as early as 7-8 hr postinfection. EBNA was detected 14 hr after the infection of pokeweed mitogen-stimulated cord blood lymphocytes with B95-8; P3HR-1 did not induce EBNA in these cells up to 72 hr. The mitogen had no effect on the expression of EBNA or EA in BJA-B cells or on the expression of EA in Raji cells. P3HR-1 induced EA in Raji cells as early as 7-8 hr after superinfection; EA was induced in BJA-B cells only after 20 hr. B95-8 did not induce EA in these cells. Experiments with phosphonoacetic acid indicated that EBV DNA replication is not necessary for the synthesis of both EBNA and EA in EBV genome-negative (BJA-b) and genome-positive (Raji) cells. These findings suggest that EBNA is the first EBV-induced intracellular antigen to appear in an EBV-infected cell and that the blast state may play an important role in the early induction of EBNA in cord blood lymphocytes. Furthermore, the resident EBV genome in Raji cells may contribute to the early expression of EA following superinfection with P3HR-1 EBV through some unknown mechanism. (24 refs.)

78-0417 **Chromosome Analysis of Seven Continuous Macaques and Baboon Hemopoietic Cell Lines Producing Herpesvirus EBV and Oncornavirus C.** (Rus) Markaryan, D. S. (Inst. Experimental Pathology and Therapy, Sukhumi, USSR); Gvaramiya, I. A.; Agrba, V. Z.; Vasilieva, V. A.; Sanguliya, I. A.; Timanovskaya, V. V. *Vopr Virusol* (6): 724-730; 1977.

The results of the karyotypic analysis of seven continuous (*Macaca arctoides*) macaque and baboon (*Papio hamadryas*) cell lines producing herpesvirus, Epstein-Barr virus (EBV), and oncornavirus C are presented. There were four lines pro-



ducing oncornavirus C (fibroblastoid Su-1 and Su-2 cultures derived from the peripheral blood cells of female baboons, KKKA-1 and KMMA-2 derived from bone marrow cells of stillborn macaques) and three lines producing EVB (lymphoblastoid KMPG-1 culture derived from baboon bone marrow and SPG-2 and SPG-3 cultures derived from baboon spleen). Although the lines differed in the degree of aneuploidy (69.6% in Su-1 compared to 14.5% in SPG-2), different lines contained similar chromosome markers:  $M_1$  in Su-1 and KMMA-2,  $M_2$  in KMPG-1 and SPG-2. (11 refs.)

**78-0418 Mechanism of the Establishment of Epstein-Barr Virus Genome-containing Lymphoid Cell Lines from Infectious Mononucleosis Patients: Studies with Phosphonoacetate.** (Eng) Rickinson, A. B. (Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England); Finerty, S.; Epstein, M. A. *Int J Cancer* 20(6): 861-868; 1977.

Experiments in which infectious mononucleosis (IM) WBC were cultured in the presence of disodium phosphonoacetate (PA) are described. At 50-150  $\mu\text{g}/\text{ml}$ , PA reduced the synthesis of infectious Epstein-Barr virus (EBV) in a producer cell line (B95-8) to 1% of control values, but it did not affect the growth of EBV-transformed cells in a 12-wk colony-forming assay. When total mononuclear cells or T-lymphocyte-depleted mononuclear cells from the blood of acute IM patients were cultured in the presence of 50  $\mu\text{g}/\text{ml}$  PA, the establishment of EBV genome-containing cell lines seen in control cultures was not observed. When T-lymphocyte-depleted IM mononuclear cells were cocultivated with fetal cells of the opposite sex, transformation occurred within a few weeks in all cocultures from each IM cell:fetal cell combination in normal medium. Transformation did not occur in any of the PA-treated cocultures from 3/5 IM cell:fetal cell combinations; in the other two cases, transformed foci appeared in the occasional coculture after considerable delay. These results suggest that all cell lines derived from the blood of IM patients are initiated in culture by a two-step process of virus release and secondary infection. They argue against the occurrence of any direct outgrowth of IM cells transformed by the virus. (30 refs.)

**78-0419 Replication of EBV in Epithelial Cells During Infectious Mononucleosis.** (Eng) Lemon, S. M. (Div. Infectious Disease, Dept. Medicine, Univ. North Carolina, Chapel Hill, NC 27514); Hutt, L. M.; Shaw, J. E.; Li, J. L.; Pagano, J. S. *Nature* 268(5617): 268-270; 1977.

Epithelial cells from the oropharynx of patients with infectious mononucleosis and high antibody titers to Epstein Barr virus (EBV) early antigen and viral capsid antigen were studied for EBV replication. Labeled EBV complementary RNA

was used in the hybridization assay. Cells from an EBV-negative donor showed little hybridization, but specimens containing transforming virus showed a much higher degree of hybridization in almost all cells. Much more striking, however, was the appearance of dense accumulations of label in a minority of the cells, often in close proximity to cells hybridizing far less RNA. The density of label was uniform over most of the infected cells, but occasionally there were denser accumulations of grains over the nucleus. The concentration of label over the most positive of these cells was equivalent to that seen in P3HR-1 cells, which replicate EBV DNA and produce virus. These findings indicate that EBV infects and replicates within epithelial cells during infectious mononucleosis. (24 refs.)

**78-0420 Epstein-Barr-Virus Immunity and Tissue Distribution in a Fatal Case of Infectious Mononucleosis.** (Eng) Britton, S. (Dept. Infectious Diseases, Danderyd Hosp., 18203 Stockholm, Sweden); Andersson-Anvret, M.; Gergely, P.; Henle, W.; Jondal, M.; Klein, G.; Sandstedt, B.; Svedmyr, E. *N Engl J Med* 298(2): 89-92; 1978.

A 3-yr-old girl who died of infectious mononucleosis had a considerable number of Epstein-Barr virus (EBV) nuclear antigen-positive cells in the thymus, spleen, and tonsils. Specific cytotoxic cells against the target cells carrying the virus were present only in the lymph nodes. Serologic tests indicated antibody patterns characteristic of a current primary infection with EBV. Extracellular DNA from the thymus, lymph nodes, spleen, and tonsils hybridized with EBV complementary RNA, resulting in two to three EBV genome equivalents/cell. Although the exact cause of death was unknown, infection with EBV can have an invasive course although host immunity is present. (14 refs.)

**78-0421 Acid Phosphatase Isoenzyme Patterns in Epstein-Barr Virus DNA-Positive Permanent Lymphoid Cell Lines.** (Ger) v. Heyden, H. W. (Medizinische Universitätsklinik Tübingen, Otfried-Müller-Strasse, D-7400 Tübingen, W. Germany); Weber, R.; Stuckstedte, H.; Sauer, J. G.; Fresen, K. O. *Blut* 35(5): 395-404; 1977.

The acid phosphatase isoenzyme pattern of several permanent B-cell lines positive for Epstein-Barr virus (EBV) DNA were determined. Several lines contained tartrate-resistant acid phosphatase. Tartrate-resistant isoenzyme 5 with components a and b could be demonstrated in monocytes, lymphocytes, chronic lymphatic leukemia cells, hairy cells, and in cells derived from a healthy donor. Acid phosphatase isoenzyme 4 was demonstrated by gel electrophoresis in separated lymphocytes; isoenzyme 4 was demonstrated in separated macrophages, but it could not be detected in all cell lines. It



suggested that the lines in which isozyme 4 could not be demonstrated were of lymphocytic origin. Cell lines with isozyme 4 could be the result of a facultative hybridization between lymphocytes and monocytes. Acid phosphatase profiles in virus-negative cell lines (Ramos, BJAB) were not significantly altered by conversion of the cells with EBV. (28 refs.)

78-0422 **Possibility of EB Virus Preferentially Transforming a Subpopulation of Human B Lymphocytes.** (Eng) Steel, C. M. (MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh, Scotland); Philipson, J.; Arthur, E.; Gardiner, S.; Newton, M. S.; McIntosh, R. V. *Nature* 270(5639): 729-731, 1977.

The major classes of immunoglobulin (Ig) heavy and light chains secreted by lymphoblastoid cell lines [established from peripheral human blood lymphocytes by transformation with Epstein-Barr virus (EBV)] were analyzed in relation to the age and clinical status of the donor. This was done to examine the possibility that EBV induces the proliferation of minor subpopulation of B cells that has already begun to secrete Ig and does not stimulate Ig synthesis de novo. Of 50 unselected lines derived from cord bloods, 49 secreted only IgM. This is in keeping with the view that EBV induces proliferation of those rare cells that are actively secreting Ig, because in the first few weeks after birth, the healthy human infant syn-

thesizes IgM exclusively. IgM secretors seem to be relatively overrepresented among the monoclonal lines derived from healthy adults and underrepresented among those from infectious mononucleosis patients. Since infectious mononucleosis is characterized by a substantial increase in serum Ig's of all three major classes, the population of Ig-secreting cells in the circulation is likely to be markedly disturbed. If this is the population that gives rise to lymphoblastoid lines, a deviation from the normal distribution of G, M, and A secretors would not be unexpected. That there is preferential, if not exclusive, transformation of those cells already secreting Ig in vivo seems to be more compatible with the data than the proposition that EBV acts as a polyclonal B-cell mitogen. (29 refs.)

*See also:*

\*(Rev.): 78-0073, 78-0074, 78-0075, 78-0076, 78-0077, 78-0078, 78-0079, 78-0080, 78-0087.

\*(Chem.): 78-0151, 78-0229.

\*(Immun.): 78-0424, 78-0433, 78-0435, 78-0436, 78-0438, 78-0439, 78-0445, 78-0451.

\*(Path.): 78-0479, 78-0488, 78-0491, 78-0527.



- 78-0423 **In Vitro Immune Responses to PPD, Extracts from Raji Cells and Nasopharyngeal Carcinoma Biopsies in NPC Leucocytes.** (Eng) Ng, W. S. (Dept. Microbiology, Univ. Hong Kong, Hong Kong); Ng, N. H.; Ho, H. C.; Lamelin, J. P. *Br J Cancer* 36(6): 713-722; 1977.

The blast transformation (BT) and migration inhibitory factor (MIF) assays were used to measure the responses of peripheral WBC from 24 patients with nasopharyngeal carcinoma (NPC) and 20 patients with other cancers (OC) to purified tuberculin protein derivative (PPD), Raji cell extracts (TS and ES), and NPC biopsy extracts (2PE and 12 PE). The NPC and OC patients did not differ in their cell-mediated immune responses (CMI) to PPD, but they did differ in their responses to the Raji cell and NPC biopsy extracts. Significantly more NPC patients had positive MIF responses to all four extracts and positive BT responses (measured in terms of stimulation indexes rather than <sup>3</sup>H-thymidine incorporation) to the Raji cell extracts only. BT responses alone were also measured in 80 NPC patients, 57 OC patients, and 15 healthy subjects. Significantly more NPC patients than controls showed positive response to each of the four extracts; however, within the NPC group, a positive response to the NPC biopsy extracts was more frequent in patients with Stage III or IV disease than in those with Stage I or II disease. These results support the existence of NPC-related CMI and indicate that positive BT responses to biopsy extracts are strongly associated with the later stages of the disease. (30 refs.)

- 78-0424 **Secondary Cytotoxic Response In Vitro Against Moloney Lymphoma Cells Antigenically Altered by Drug Treatment In Vivo.** (Eng) Santoni, A. (Lab. Experimental Chemotherapy, Drug Res. and Development Program, Div. Cancer Treatment, NCI, NIH, Public Health Service, US Dept. Health, Education, and Welfare, Bethesda, MD 20014); Kinney, Y.; Goldin, A. *J Natl Cancer Inst* 60(1): 109-112; 1978.

The cell-mediated cytotoxic response in vitro to a Moloney strain of murine leukemia virus-induced tumor (LSTRA) altered by 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC) was investigated with the use of mixed leukocyte-tumor cell cultures (MLTC). Primary stimulation of BALB/cCr spleen cells by LSTRA/DTIC did not generate cytotoxic lymphocytes against either the parental LSTRA, LSTRA/DTIC, or an unrelated RBL-5 line. However, when C57BL/6 (H-2b) allogeneic spleen cells were used as stimula-

tors, high cytotoxic responses were obtained against H-2b RBL-5 lymphoma cells. Cytotoxic activity against LSTRA/DTIC cells was obtained when spleen cells collected from mice presensitized with LSTRA/DTIC cells were cocultured with the same lymphoma line (secondary response). A secondary in vitro response was also obtained with the use of parental as well as LSTRA/DTIC cells as stimulators in coculture with spleen cells of LSTRA/DTIC-sensitized donor inbred BALB/c mice. Thus, a partial cross-reactivity was found between the LSTRA and LSTRA/DTIC tumor lines. (12 refs.)

- 78-0425 **Splenic Role in the Regulation of Immune Responses.** (Eng) Romball, C. G. (Dept. Immunopathology, Scripps Clinic Res. Foundation, La Jolla, CA 92037); Weigle, W. O. *Cell Immunol* 34(2): 376-384; 1977.

Evidence that the spleen has a role in regulating antibody production in other lymphoid organs was provided by the cyclic fluctuations of spleen plaque-forming cells (PFC) that occurred in New Zealand rabbits given a single iv injection of aggregated human  $\gamma$ -globulin. The PFC arose simultaneously in mesenteric lymph nodes, peripheral blood, and spleen; they appeared to be derived from the spleen since splenectomy prior to antigen injection abrogated these responses. Furthermore, a noncyclic appearance of PFC in popliteal nodes of rabbits responding to sc antigen injection was converted to a cyclic response by simultaneous iv antigen injection, an effect that was abolished by prior splenectomy. It is suggested that following iv antigen injection, suppressor cells and antibody-forming cells are activated in the spleen and disseminated to other lymphoid tissue. (22 refs.)

- 78-0426 **Host Serum Factors Versus Tumor Factors in Immune Resistance to Metastases.** (Eng) Vaage, J. (Dept. Cancer Therapy Development, Pondville Hosp. Walpole, MA 02081). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P. Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy Vol. 5, 517 pp.; 305-318; 1977.

The role of immune serum factors, presumably antibodies in resistance to vascular dissemination of tumor growth and



The influence of excess free tumor antigens on antitumor transplantation immunity were studied in a methylcholanthrene-induced fibrosarcoma and a spontaneous mammary carcinoma, both syngeneic in C3H mice. After irradiation, related injections of immune serum plus normal lymph node cells protected the mice against pulmonary metastases following injection of fibrosarcoma cells. Injections of immune serum and normal lymphocytes did not protect irradiated mice against sc injection of fibrosarcoma cells. A second study compared pulmonary and sc immune resistance against implanted mammary carcinoma cells. During progressive growth of the primary tumor implant, concomitant antitumor immunity reached a higher level of effectiveness in the lungs than in sc tissues. The concomitant immune resistance declined under the burden of a tumor implant that had become > 10 mm. The immune resistance against tumor cells injected iv remained effective longer, however, under the same burden than did resistance against tumor cells injected sc. A third study investigated the opposing influences of antigen and antibody, present in the blood of an animal at the same time, on resistance to implanted tumor cells. The results indicate that immune serum can be effective against tumor cells injected into the bloodstream and against excess tumor antigens free in the circulation. Humoral factors, therefore, may be of particular importance in preventing metastases directly by cytotoxic effects, as well as indirectly neutralizing the growth-promoting effects of tumor antigen overload. (15 refs.)

78-0427 **Reversible Suppression of Malignancy and Differentiation of Melanoma Cells.** (Eng) Silagi, S. (Genetics Lab., Dept. Obstetrics Gynecology, Cornell Univ. Medical Coll., New York, NY 10021). *Am J Pathol* 103(3): 671-684; 1977.

Nontumorigenicity was reversibly suppressed in two clones of B16 melanoma cells grown with 5-bromodeoxyuridine (BUdR). The nontumorigenic cells were immunogenic, and when C57BL/6J mice were inoculated with the cells, they were resistant to challenge with the parental, untreated syngeneic tumor cells. A mixture of a highly immunogenic clone, B16, and malignant cells was also nontumorigenic. These effects are related to the host immune response, since they occurred only in immunocompetent mice. BUdR also reversibly suppressed functions related to pigment formation and melaninogen activation. These effects required incorporation of BUdR into DNA, emphasizing the value of this thymidine analog for studies of the normal regulation of gene activity and the perturbations that lead to malignancy. (21 refs.)

78-0428 **Suppressors in the Network of Immunity.** (Eng) Siegal, F. P. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021). *N Engl J Med* 298(2): 102-107; 1978.

The nature of suppressor cells involved in the physiologic inhibition of the immune response, the distinction between these cells and autoimmune cells, and interactions between the suppression of B-cell differentiation and antibody production by subsets of T cells are discussed. (11 refs.)

78-0429 **Non-immunological Enhancement of Tumour Transplantability in X-irradiated Host Animals.** (Eng) Jamasbi, R. J. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); Nettesheim, P. *Br J Cancer* 36(6): 723-729; 1977.

The frequency of tumor takes and growth rates were compared in normal and thymectomized, x-irradiated, immunologically suppressed male DBA/2 (H-2d) mice. The mice were thymectomized and given a single dose of 600 rads' whole-body x-irradiation 2 wk later; 48 hr after irradiation, the animals received  $10^3$  or  $10^4$  live MSC-10 tumor cells. Only 50% of the sham-operated, unirradiated mice given a  $10^4$  inoculum developed tumors compared to 100% of the thymectomized, x-irradiated mice. Mortality incidence followed similar trends. A dose of  $10^3$  cells failed to produce tumors in controls, but it did so in 70% of the thymectomized, x-irradiated mice. Thymectomized and sham-thymectomized x-irradiated mice had severe impairment of the humoral immune response, as measured by the hemagglutinin assay. Thymectomized, irradiated mice that were reconstituted ( $2 \times 10^4$  syngeneic spleen cells and thymic implants within 24 hr of irradiation) still had marked impairment of the humoral immune response. Reconstituted animals had a similar response to tumor challenge as did the other irradiated groups. In a test of immunocompetence and resistance to tumor transplantation 6 wk after whole-body x-irradiation, partial recovery of the hemagglutinin response was observed in all but the thymectomized, x-irradiated mice. These findings indicate that nearly all animals had reacquired an almost normal degree of resistance to tumor cell inoculation. The occurrence of metastases was not affected by the immunosuppressed state. (9 refs.)

78-0430 **Osteotropism of Human Breast Cancer.** (Eng) Bockman, R. S. (Lab. Calcium Metabolism, Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Myers, W. P. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 431-450; 1977.

Factors that may lead to the implantation and growth of bone metastasis from breast carcinoma and some of the metabolic disturbances associated with these lesions are considered. Serum immunoreactive parathyroid hormone (iPTH) and prostaglandin E (PGE) are elevated in subpopulations of



breast cancer patients. No evidence of immune cell dysfunction was found when in vitro tests were carried out on a similar group of breast cancer patients compared to normals. Immune cell-derived PGE and lymphokines such as osteoclast-activating factor could have significant biological consequences and yet be unmeasured by gross cell counts. PGE was measured in most of the tumor-conditioned media studied, but its source could not be conclusively attributed to the cancer cells, since the tissues represent a heterogeneous population of normal and malignant cells. Significant osteolytic activity was demonstrated in the lymphocyte-conditioned media (LCM) of 11/11 breast cancer patients studied. The unstimulated LCM activities of breast cancer patients differed significantly from the unstimulated LCM of normal controls. No significant difference was noted between normals and 11 patients with a variety of cancers whose disease was associated with a low incidence of bone metastasis. The chemical nature of the LCM osteolytic activity is unknown. The finding of a probable lymphokine that may cause osteolysis to occur in breast cancer patients at significant risk for bone metastases is felt to be relevant to the osteotropism of this cancer and to lend support to the concept of tumor recruitment and/or subversion of host defense mechanisms to the detriment of the host. (49 refs.)

**78-0431 Early Arrest of Circulating Tumor Cells in Tumor-bearing Mice.** (Eng) Graves, D. (Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263); Weiss, L. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 175-184; 1977.

The questions of whether host sensitization by tumor bearing affects the initial arrest patterns of circulating cancer cells and whether any such alterations are immunospecific were examined in two murine tumor systems. A methylcholanthrene-induced fibrosarcoma was maintained by serial transplantation in syngeneic C3H/HeHa mice, and an estradiol-induced 6C3HED lymphosarcoma was serially passaged in syngeneic C3H/StHa hosts. Both tumor types evoked humoral and cell-mediated immune responses upon sc injection into their respective hosts. Early arrest patterns were determined with iv-injected radiolabeled tumor cells. In fibrosarcoma-bearing mice, the percentage of injected radioactivity recovered in the lungs was much less in tumor-bearing animals than in normal, non-tumor-bearing mice, but that in the liver was much greater. There was a tendency toward greater localization of radiolabeled cells in the lungs of lymphosarcoma bearers and less clear-cut differences in arrest in the liver; however, these alterations in arrest patterns were not comparable in magnitude to those seen in the fibrosarcoma-bearing mice. In another series of experiments, mice bearing tumors to which they were sensitized were inoculated with a second tumor of different etiology, and subsequent early arrest patterns were determined. The fibrosarcoma and lymphosarcoma were also used in this study. The results indicate that the shifts in localization patterns in tumor-bearing mice

observed originally were mediated by host defense reactions. These results suggest that previous work on tumor cell arrest, which usually involved the iv injection of cancer cells into normal, non-tumor-bearing animals, may have used an unrealistic model for the study of arrest patterns. (27 refs.)

**78-0432 Quantitative Analysis of Tumor:Host Interaction and the Outcome of Experimental Metastasis.** (Eng) Fidler, I. J. (Basic Res. Program, NCI and Frederick Cancer Res. Center, Frederick, MD 21701); Gersten, D. M.; Riggs, C. W. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 277-303; 1977.

The effects of immune manipulation on the arrest, distribution, and survival of low- and high-metastases variants of B16 melanoma were examined after iv injection into immune-competent and -incompetent syngeneic and allogeneic hosts. The initial arrest in the pulmonary bed neither correlated with nor predicted the survival of tumor cells and their subsequent growth into visible tumor colonies. In every experiment, the B16-FFO (high-metastasis) cell line formed significantly more lung tumors than the B16-F1 (low-metastasis) line, independent of the immune status of the host, demonstrating that immune status or manipulation did not eliminate differences in biological properties. Host properties such as tumor immunity, however, quantitatively modified tumor cell arrest and survival. The findings indicate that allogeneic animals are not appropriate model systems for study of the metastatic sequence and that the initial arrest of tumor cells in organs and tumor cell survival and growth are probably influenced by both tumor cell properties and multiple host factors. Animals sensitized to a tumor exhibited kinetic patterns of tumor cell arrest and survival that differed from those of normal syngeneic hosts. Successfully immunized or unsuccessfully immunized (tumor-sensitized) animals might be a more suitable model for studies of experimental cancer metastasis than normal animals. (37 refs.)

**78-0433 Patterns of Metastases in Hemopoietic Neoplasms: Immunologic Correlations.** (Eng) Iochim, H. L. (Dept. Pathology, Lenox Hill Hosp., New York NY 10032); Pearce, A.; Keller, S. E. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 333-345; 1977.

The role of immunity in the occurrence, timing, and distribution of metastases of several lines of hemopoietic tumors was explored in W/Fu rats. Tumor cells that expressed strong



membrane antigenicity were recognized and destroyed by the immune system of competent hosts. Despite their antigenicity, these tumor cells could proliferate and metastasize unrestrictedly in immunologically deficient hosts such as infants and immunosuppressed (x-irradiated) adults. The distribution of metastases was also investigated with two types of leukemic cells: (1) Gross leukemia virus (GLV)-induced W/Fu rat leukemic cells expressing surface murine leukemia virus-associated (MuLV+) membrane antigens; and (2) dimethylbenz(a)anthracene (DMBA)-induced W/Fu rat leukemic cells. Invariably, when transplanted, GLV-induced leukemic cells metastasized to the thymus and lymph nodes, whereas DMBA-induced leukemic cells formed liver and spleen tumors. These characteristic patterns of dissemination remained constant regardless of route of injection (iv or sc), and they were reproduced in infant and x-irradiated recipients. The persistence of this specific distribution in immunosuppressed hosts indicates that the localization of circulating tumor cells depends on intrinsic cellular properties that determine their preferential growth in certain tissues. Although the local growth and metastatic potential of a tumor may depend on immune surveillance, the site of metastasis is conditioned by genetic cellular qualities that determine the compatibility between tumor cell and microenvironment. (37 refs.)

**78-0434 Role of T and B Lymphocytes in the Development and Growth of Experimental Metastases.** (Eng) Yuhas, J. M. (Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM 87131). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, G., eds. (New York: Raven Press): Vol. 5, 517 pp.; 347-372; 1977.

The role of T and B lymphocytes in spontaneous and artificial metastasis (iv injection of large numbers of tumor cells) was compared using 4-mo-old female BALB/c mice and line 1 carcinoma cells. Exposure of the mice to 500 rads of x-rays prior to sc transplant of the carcinoma accelerated the appearance of spontaneous metastases by 1 wk. In the artificial metastasis system, the same exposure increased the number of detectable lung tumor colonies by factors of 5 to 20. Spleen lymphocytes from immunized mice reversed the radiation-induced enhancement of metastasis in both systems. Total spleen lymphocyte inocula were compared with T- and B-lymphocyte inocula for ability to reverse radiation-induced enhancement of both types of metastasis. In the spontaneous metastasis, the B-lymphocyte inocula was as effective in reversing the radiation effect as was the total inocula, but the T-lymphocytes had no detectable effect. In the artificial metastasis system, T lymphocytes were effective but B lymphocytes were not. It is concluded that the primary immunologic effector involved in the control of spontaneous metastases is the B lymphocyte and that the T lymphocyte is the major effector involved in the control of artificial metastases. Studies conducted with the artificial metastasis system may yield misleading information regarding the relative importance of B- vs T-lymphocyte control. (3 refs.)

**78-0435 Tumour Cell Lines Induce Interferon in Human Lymphocytes.** (Eng) Trinchieri, G. (Institut Suisse de Recherches Experimentales sur le Cancer, CH-1066 Epalinges, S. Lausanne, Switzerland); Santoli, D.; Knowled, B. B. *Nature* 270(5638): 611-613; 1977.

The production of interferon by various human cell lines upon contact with human lymphocytes was investigated. Two simian virus 40 (SV40)-transformed brain cell cultures, two colorectal carcinomas, five melanomas, one rhabdomyosarcoma, and one cervical carcinoma induced high levels of antiviral activity when cultured with human lymphocytes. The supernatant from the cultures alone or the lymphocytes alone did not possess this activity, nor did 12 human fibroblast lines from normal tissue, 13/15 SV40 transformed lines and 5 tumor derived lines. This virus inhibitor was considered to be interferon. Testing of several mouse cell lines indicated that some were positive for interferon production (data not shown). The kinetics of interferon production were similar to those observed after virus infection of lymphocytes. This stimulus for interferon production by lymphocytes on incubation with cell lines is unknown, but contact between lymphocytes and cells appears to be required. Interferon production was probably not the result of allogeneic or xenogeneic antigens on the cell surfaces. The ability of interferon to enhance specific and nonspecific cell-mediated cytotoxicity, as well as its inhibitory effect on tumor cell growth, could be responsible for the antitumor effect observed in vivo with exogenous interferon and interferon inducers. (26 refs.)

**78-0436 Specific Triggering by Concanavalin A of a Secondary T Killer Cell-mediated Anti-tumor Immune Response.** (Eng) Reme, T. X. (Dept. Clinical Immunology, Centre Paul Lamarque, Hopital St. Eloi, 34 033, Montpellier, France); Gomard, E.; Levy, J. P. *Cell Immunol* 34(2): 299-309; 1977.

Spleen cells from C57 Bl/6 mice that rejected a Moloney sarcoma virus (MSV)-induced tumor elicited a strong cytolytic reaction against MSV-associated antigens when incubated for 7 days with a mitogenic dose (5 µg/ml) of concanavalin A (Con A). The cytolytic activity as evaluated in a chromium release test was mediated by T lymphocytes and anti-Thy 1-2 serum treatment; it was independent of residual Con A since treatment with n-[α-methyl]mannopyranoside did not modify the reaction. A similar reactivity was obtained with phytohemagglutinin at mitogenic doses but not with the B-cell mitogen lipopolysaccharide. This secondary like response was regenerated up to 50 days post-MSV inoculation but decreased regularly. The cytolytic activity had an antigenic pattern indistinguishable from that of the relevant tumor cell reactivation and was directed by the same H-2 restriction. (31 refs.)

**78-0437 Role of Non-conventional Natural Killer Cells in Resistance Against Syngeneic Tumour Cells**



**in Vivo.** (Eng) Haller, O. (Dept. Immunology, Uppsala Univ. Medical Sch., Box 582, S-751 23 Uppsala, Sweden); Hansson, M.; Kiessling, R.; Wigzell, H. *Nature* 270(5638): 609-611; 1977.

The role of natural killer (NK) cells in resistance against challenge by the YAC Moloney lymphoma of A/Sn genotype was investigated. (A/Sn x 129/J) F<sub>1</sub> animals were irradiated and repopulated with bone marrow cells from high or low NK donors that were histocompatible with the recipient and tumor cells used. 'High' NK hybrids had significantly higher resistance than 'low' hybrids following transplantation with 10<sup>5</sup> YAC cells. Increasing the dose to 10<sup>6</sup> cells resulted in the death of all animals. Repetition of the experiment using (A/Sn x C57BL/6) F<sub>1</sub> animals that had been thymectomized showed that high NK marrow donors provided the same high resistance as in the previous experiment. Thus thymectomy had no effect on the results. There was a dramatic drop in NK induced resistance between 6 wk and 6 mo of age, corresponding to the reduction of in vitro NK activity. These findings suggest that natural resistance against tumor outgrowths in vivo may be the result of a non-conventional cell type. (19 refs.)

**78-0438 Studies of the Mechanisms for the Induction of In Vivo Tumor Immunity. II. Distribution and Homing of Cytotoxic Effector and Precursor Cells.** (Eng) Ting, C. C. (Lab. Cell Biology, NCI, NIH, Public Health Service, U. S. Dept. Health, Education, and Welfare, Bethesda, MD 20014). *J Natl Cancer Inst* 60(2): 437-444; 1978.

Cytotoxic T (thymus) lymphocytes (CTL) with specific cytotoxicity against the leukemia-associated antigens of FBL-3, a syngeneic Friend virus-induced leukemia in C57BL/6 mice, could be adoptively transferred to sublethally x-irradiated (350 R) syngeneic hosts and could be induced by adoptive transfer of either normal or presensitized lymphocytes obtained from immunocompetent hosts. The CTL and their precursor cells were systemically distributed in peripheral lymph nodes and spleen, although they tended to home to lymphoid tissue of the same origin. Direct cytotoxicity was obtained with the lymphocytes from these lymphoid tissues, and cells from these lymphoid tissues could produce secondary cytotoxic responses by the mixed lymphocyte tumor cell culture reactions 40-60 days after adoptive transfer. In addition, lymph node and spleen cells had a synergistic effect on cytotoxicity induction. These findings indicate that tumor immunity was widely distributed and that various lymphocyte populations were involved in the generation of efficient cell-mediated cytotoxic responses. (21 refs.)

**78-0439 Natural Cytotoxic Reactivity of Rat Lymphocytes Against Gross Virus-induced Tumor Cell Lines as Measured by [<sup>125</sup>I]Iododeoxyuridine and Tri-**

**tiated Proline Microcytotoxicity Assays.** (Eng) Oldham, R. K. (Lab. Immunodiagnosis, Div. Cancer Biology and Diagnosis, NCI, NIH, Bethesda, MD 20014); Ortaldo, J. R.; Herberman, R. B. *Cancer Res* 37(12): 4467-4474; 1977.

The ability of mononuclear cells from W/Fu rat spleens to mediate natural cytotoxicity against a syngeneic Gross virus-induced lymphoma is reported. These naturally cytotoxic cells, designated N cells, appear to be lymphocytes that lack both detectable immunoglobulin (Ig) and complement receptors and, therefore are not mature B cells. They differ from the classic null cells, which have Ig and/or complement receptors. The N cells were present in normal spleens and in spleens from immunized animals. The same cell subpopulation responsible for natural activity in short-term <sup>51</sup>Cr-release assays was also responsible for natural activity in long-term <sup>125</sup>I-iododeoxyuridine-release assays. In addition, the mononuclear cells were active against both nonadherent cell and monolayer targets. The natural activity measured by the long-term assays appeared to be somewhat less age-specific than that reported previously with the <sup>51</sup>Cr assay. Appropriate base lines are described in an attempt to better document natural activity in these assays. This natural activity must be closely monitored in any system purporting to measure cell-mediated cytotoxicity. (37 refs.)

**78-0440 Possible Relationship of Plasma IgA, IgG, and IgM to Breast Cancer in British and Japanese Women.** (Eng) Wang, D. Y. (Dept. Clinical Endocrinology, Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London, WC2A 3PX, England); Goodwin, P. R.; Bulbrook, R. D.; Hayward, J. L.; Abe, O.; Utsunomiya, J.; Kumaoka, S. *Eur J Cancer* 13(12): 1405-1409; 1977.

Plasma IgA, IgG, and IgM levels were determined in 22 Japanese (J) and British (B) adolescent girls, 35 adult B women, 37 adult J women, 22 B patients with breast cancer, and 30 J patients with breast cancer. There was no statistical difference in plasma IgA levels in normal B and J women, and the levels in adolescents did not differ from those in adults. The levels of IgG and IgM were significantly higher in J women than B women. Levels in J and B adolescents were similar to those in adults of the same race except for IgG: Japanese adolescents had significantly lower IgG levels than adults. Levels of IgA and IgG in J women with breast cancer were comparable to those in normal J women, but the IgM level in these patients were significantly below normal. IgM levels in J women with breast cancer were similar to those in B patients and normal B women. Levels of IgA, IgG, and IgM did not significantly differ between normal B women and B women with breast cancer. (23 refs.)

**78-0441 Characterization of the Fc Receptors of the Murine Leukemia L1210.** (Eng) Cooper, S. M. (Clinical Immunology and Rheumatic Disease Section, Dep



Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA 90033); Sambray, Y. *J Supramol Struct* 6(4): 591-597; 1977.

A glycoprotein extract prepared from the plasma membranes of L1210 cells [a carcinogen-induced leukemia derived from DBA/2 mice that lacks surface immunoglobulin (Ig) but bears an Fc receptor] was subjected to affinity chromatography on columns of Sepharose 4B to which either heat-aggregated human IgG or F(ab')<sub>2</sub> fragments had been covalently coupled. The intact IgG column bound 35.7% of the applied labeled preparation, whereas the F(ab')<sub>2</sub> column bound only 2.8%. About 75% of the bound glycoproteins were eluted with citrate buffer. Three peaks with apparent mol wts of 65,000, 45,000, and 28,000 daltons were identified and purified by electroelution from polyacrylamide gels. The isolated proteins were able to bind to the same subclasses of mouse myeloma proteins as the intact L1210 cells, indicating that these molecules are related to L1210 surface Fc receptors. Amino acid analyses of the three proteins were very similar, suggesting that the observed molecular heterogeneity might be due to carbohydrate differences. Neuraminidase digestion of the isolated proteins resulted in mobility shifts in polyacrylamide gel electrophoresis that were consistent with the interpretation that either the isolated proteins have considerably different sialic acid contents or that removal of the sialic acid results in disaggregation of an Fc receptor molecule. (17 refs.)

78-0442 **Continuous Lymphoblastoid Suspension Cultures from Cells of Haematopoietic Organs of Baboons with Malignant Lymphoma. Report III. Immunological Studies.** (Eng) Kokosha, L. V. (Inst. Experimental Pathology and Therapy, P. B. 66, Gora Trapetziya, Sukhumi, USSR); Agrba, V. Z.; Lapin, B. A.; Yakovleva, L. A.; Arshina, N. N.; Markova, T. P.; Pimanovskaja, V. V. *Exp Pathol (Praga)* 13(4/5): 247-254; 1977.

Suspension cultures (KMPG-1, SPG-2, and SPG-4) from the haematopoietic tissue of *Papio hamadryas* monkeys with lymphoma were studied immunologically. B-95-8 cells [marmoset lymphocytes transformed in vitro by Epstein-Barr virus (EBV)] were used as controls. Direct immunofluorescence revealed surface immunoglobulin (Ig) in B-95-8 and KMPG-1 cells (the other two lines were not investigated). All lines produced cytoplasmic Ig and IgM; B-95-8 and SPG-4 produced IgG. Rosette-formation studies revealed no markers on T cells. Indirect immunofluorescence, using serum from Burkitt's lymphoma patient with an antibody titer to EBV capsid antigen equal to 1:320, showed a granular cytoplasmic reaction in all lines. The percentage of positively reacting cells varied from 2% to 6% in the lymphoma lines and 3% to 5% in the B-95-8 cells; these findings correspond to the number of herpes-type particles observed electron microscopically. Titration of sera from the suspension cultures and the Burkitt's lymphoma patient revealed cytoplas-

mic antigens in both the homologous and heterologous cultures. The mean geometrical EBV titers in baboons living in the wild and lymphomatous baboons from the colony supplying the cultures were 1:3.1 and 1:120, respectively. These results indicate that the herpesvirus of baboons is immunologically similar to EBV. (45 refs.)

78-0443 **Suppression of Myeloma Growth in Vitro by Anti-idiotypic Antibodies: Inhibition of DNA Synthesis and Colony Formation.** (Eng) Schreiber, H. (Dept. Pathology, La Rabida-Univ. of Chicago Inst., Univ. Chicago, East 65th St. at Lake Michigan, Chicago, IL 60649); Leibson, P. *J Natl Cancer Inst* 60(1): 225-233; 1978.

The effect of anti-idiotypic antisera on myeloma cell growth in vitro was investigated. Antibodies against S107 myeloma protein inhibited DNA synthesis and colony formation on S107 myeloma cells in soft agar. Variant subclones of the myeloma differed in the density of surface immunoglobulin (Ig) and the amounts secreted. The different sublines had different sensitivities to anti-idiotypic antibody and complement. Colony formation of myeloma cells with a high density of surface idiotype was strongly inhibited; however, the antibody only moderately suppressed growth of myeloma cells with a reduced density of cell-surface idiotype. The differences in the expression of membrane-bound idiotype between the sublines correlated with the differences in the secretion of Ig. The effect of anti-idiotypic antibodies depended on the presence of complement or normal spleen cells. Preincubation of the tumor cells with anti-idiotypic antibodies in the absence of complement made myeloma cells resistant to the addition of antibody and complement. Anti-idiotypic antisera were not cytotoxic. This system can be used to study tumor-escape mechanisms and to detect specific cell-surface-bound Ig markers. (31 refs.)

78-0444 **Tumor-specific Antigens on Rat Liver Cells Transformed In Vitro by Chemical Carcinogens.** (Eng) Yokota, T. (Dept. Bacteriology, Fukushima Medical Coll., Fukushima, 960 Japan); Sizaret, P.; Martel, N. *J Natl Cancer Inst* 60(1): 125-129; 1978.

Using membrane immunofluorescence and xenogeneic sera, a search was made for oncofetal antigens on rat epithelial-like liver cell lines transformed in vitro by dimethylnitrosamine and N-methyl-N'-nitro-N-nitrosoguanidine and on those transformed spontaneously. Of seven rabbit antisera, three reacted with the corresponding immunizing cell lines. One tumor-specific individual antigen and two tumor-specific cross-reacting antigens were present on the lines. These antigens were not detected in 10-, 15-, and 19-day rat fetuses or on the liver and spleen cells of normal BD adult rats, fetal liver cells, or the liver and intestinal carcinoma cells of Wistar rats. Sera from multiparous pregnant rats had no antibodies against these tumor antigens. (21 refs.)



- 78-0445 **Cytotoxicity Against Tumour-associated Antigens Not H-2 Restricted.** (Eng) Holden, H. T. (Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD 20014); Herberman, R. B. *Nature* 268(5617): 250-252; 1977.

The cytotoxicity of T cells removed from BALB/c (H-2d) or C57BL/6 (H-2b) mice inoculated im with a regressor strain of Moloney murine sarcoma virus (MSV) was investigated. Spleen cells from these mice showed a strong cytotoxic reactivity against Moloney leukemia virus (MLV)- or Rauscher leukemia virus (RLV)-induced lymphomas, the syngeneic tumor targets. Various levels of cytotoxicity were also observed against allogeneic MLV or RLV tumor cells, with the strength of the response being dependent on the strain of mouse from which the effector cells were derived. C57BL/6 spleen cells showed a strong reactivity against tumor-associated antigens on allogeneic tumors, but BALB/c effector cells were not as efficient at lysing C57BL/6 tumor targets. Cytolysis was not directed against alloantigens. There was no lysis against H-2-identical tumor cells that did not carry the appropriate antigen. It is thus suggested that the antigenic moiety against which the MSV-immune T cell is directed is not exclusively a modification of the H-2 antigen. (22 refs.)

- 78-0446 **Murine Pluripotential Stem Cells Lack Ia Antigen.** (Eng) Basch, R. S. (ICRF Tumour Immunology Unit, Dept. Zoology, Univ. Coll. London, London, England); Janossy, G.; Greaves, M. F. *Nature* 270(5637): 520-522; 1977.

The effects of antisera to I region associated (Ia) antigens on cells which give rise to spleen colonies was investigated. Findings indicated that cells identified by heterologous antiserum to mouse Ia antigens were not the product of clonal proliferation of pluripotential stem cells. Thus the cells recognized by the anti-Ia sera in human fetuses and in acute myelocytic leukemia are not related to the most immature hematopoietic elements. (20 refs.)

- 78-0447 **Isolation of a Human Teratoma Cell Line Which Expresses F9 Antigen.** (Eng) Hogan, B. (Imperial Cancer Res. Fund, Mill Hill Lab., Burtonhole Lane, London NW7, England); Fellous, M.; Avner, P.; Jacob, F. *Nature* 270(5637): 515-518; 1977.

The F9 antigen, found in early mouse embryos, spermatozoa and male germinal cells, was located on the SuSa human teratocarcinoma cell line isolated from a 30-yr-old man with testicular teratoma. Evidence suggests that SuSa cells are equivalent to the undifferentiated stem cells of human testicular teratocarcinomas. These results raise the possibility of searching for circulating autoantibodies in patients with teratoma, using lines such as SuSa as targets. (14 refs.)

- 78-0448 **Multiple Alleles of the Lyb-2 Locus.** (Eng) Shen, F. W. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Spanondis, M.; Boyse, E. A. *Immunogenetics* 5(5): 481-484; 1977.

The presence of the 2.1, 2.2, and 2.3 alleles of the *Lyb-2* alloantigen system on mouse tissues containing B cells was confirmed by spleen cell cytotoxicity assays with immune sera. The proportion of *Lyb-2*(+) cells in various cell populations and the strain distribution of the three phenotypes are shown in tables. In  $F_2$  mice, *Lyb-2.2* and *Lyb-2.3* segregated as alleles of *Lyb-2.1*. No strain had more than one *Lyb-2* specificity. All three BALB/c myelomas tested were negative for *Lyb-2*. (3 refs.)

- 78-0449 **Increase in Immunogenicity of a Pulmonary Squamous-Cell Carcinoma, Propagated In Vitro.** (Eng) Jamasbi, R. J. (Univ. Tennessee, Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); Nettesheim, P. *Int J Cancer* 20(6): 817-825; 1977.

The immunogenicity of 3-methylcholanthrene-induced nonimmunogenic pulmonary squamous cell carcinoma (MSC-10) was investigated following maintenance in vitro. The in vivo-passaged MSC-10 line was nonimmunogenic and was incapable of inducing transplantation resistance in syngeneic hosts. With increasing in vitro passage, however, the MSC-10 line gradually lost tumorigenicity in immunocompetent hosts. This was related to an increase in antigenicity since immunosuppressed hosts (thymectomy + 600 rads whole-body x-irradiation) supported the growth of tumor cells but immunocompetent hosts did not. The antigens involved in rejection are not heterologous serum proteins present in the culture media, since cells grown in isologous sera were also rejected by immunocompetent hosts. The antigen present in cultured cells appeared to be of tumor origin, because mice immunized against the in vitro tumor line showed resistance against the parental in vivo tumor line. Injection of the cultured cell line into normal or immunosuppressed hosts produced tumors with the same histological characteristics as those of the in vivo tumor line. It is concluded that the weakly antigenic carcinoma becomes more immunogenic during in vitro culture and therefore is capable of inducing transplantation resistance. This phenomenon might be of practical use in the immunotherapy of weakly immunogenic tumors if similar increases in immunogenic potency should occur in human carcinoma cells cultivated in vitro. (26 refs.)

- 78-0450 **Chemical and Immunological Studies of Cell Surfaces from Normal and Transformed Cells.** (Eng) Grimes, W. J. (Dept. Biochemistry, Univ. Arizona Coll. Medicine, Tucson, AZ 85724); Van Nest, G. A.; Kamm, A. R. *J Supramol Struct* 6(3): 449-464; 1977.



Chemical and immunological studies were performed on A<sub>31</sub> (cloned line of BALB/c 3T3 fibroblasts), c5 cells (a transformed line cloned from A<sub>31</sub>), c5T cells (isolated from tumor caused by injecting c5 cells into BALB/c mice), MSC (derived from a Moloney murine sarcoma virus-induced BALB/c mouse tumor), 3T12T cells (isolated from a tumor induced by injecting 3T12 cells into BALB/c mice), and PBC (early passage BALB/c embryo fibroblasts). The biological properties of these lines are listed. Lymphocytes from the spleens and lymph nodes of tumor-bearing mice were non-specifically cytotoxic for all the normal and transformed cells. Some of the cell lines were able to induce specific antibody formation in BALB/c hosts. Antisera specific for the transformed lines were also prepared in New Zealand white rabbits, and these could be used to determine specific surface antigens on the transformed cells. Chemical studies indicated that glycolipid alterations were present on normal cells and on, but not all, transformed lines. Electrophoresis of labeled glycoproteins indicated that there were no specific changes associated with malignancy. Chromatography of the peptides following pronase treatment showed only a few changes (high-mol-wt glycopeptides) that could be associated with malignancy. The different responses of the various lines are outlined. (45 refs.)

**78-0451 Effect of Cyclophosphamide on Syngeneic Transplantation of Adenovirus 12-transformed Tumor Cells in C3H/He Mice.** (Eng) Pauluzzi, S. (Istituto di Patologia Infettiva dell'Universita degli Studi-Policlinico, Perugia, 06100, Perugia, Italy); Merletti, L. *Boll Ist Sierot-Milan* 56(4): 310-315; 1977.

C3H/He mice were given a single ip injection of cyclophosphamide (CP, 150 mg/kg) before or after sc injection of syngeneic adenovirus-induced tumor cells (10% or 35% suspension). CP did not affect tumor evolution when injected 24 and 39 hr before cell implantation. CP injected 24 or 39 hr after implantation prevented or retarded tumor growth. In mice bearing palpable tumors, it induced complete regression in 5.7% of the animals without affecting the development of homograft immunity. These mice demonstrated complete resistance against rechallenge with tumor cells. (24 refs.)

**78-0452 Increased Expression of Actin-like Protein in Human and Ethylnitrosourea-induced Tumors of the Nervous System.** (Eng) Toh, B. H. (Dept. Pathology, Immunology, Monash Univ. Medical Sch., Melbourne, Australia); Qvist, R.; Randell, V. B.; Elrick, W. L. *Cancer Res* 37(12): 4280-4284; 1977.

Twenty-one human intracranial tumors (15 astrocytomas and 6 meningiomas) and 26 ethylnitrosourea-induced rat brain tumors (7 astrocytomas and 9 schwannomas) were

examined by indirect immunofluorescence for reactivity with a human antiactin antibody. In cryostat sections, both human and rat astrocytomas showed an increased reaction with the antiactin antibody compared with normal astrocytes, and the reaction with astrocytomas was greater than that with meningiomas. Malignant rat schwannomas also showed prominent antiactin staining, which contrasted with the negative reaction in normal Schwann cells. These in vivo observations were paralleled by concurrent studies with impression films and in vitro monolayer cultures of tumor tissue. The results, combined with data from studies of antiactin antibody reactivity with other nonneural tumors, suggest that an enhanced actin expression in vivo may be a general feature of all tumors, although more pronounced in malignant than in benign tumors. (24 refs.)

**78-0453 Immunostimulation of Chemical Oncogenesis in the Mouse.** (Eng) Prehn, R. T. (Jackson Lab., Bar Harbor, ME 04609). *Int J Cancer* 20(6): 918-922; 1977.

Thymectomized, x-irradiated female (C57BL-ICR x BALB/c-ICR)F<sub>1</sub> hybrid mice were inoculated with various amounts of normal syngeneic spleen cells and subsequently exposed to 0.05%, 0.5%, 5.0%, or 1.0% 3-methylcholanthrene (3-MC). Paraffin wafers containing 3-MC were inserted sc. Among animals exposed to a high concentration of 3-MC, there was significantly higher incidence of sarcomas among those that had received small numbers (10<sup>4</sup>) of spleen cells than among those that had received none or the max number (10<sup>7</sup>). When the 3-MC concentration was low, tumor incidence was the same in all groups, regardless of the number of spleen cells injected. Since the av immunogenicity of sarcomas has been shown to be related directly to the concentration of the chemical carcinogen and inversely to tumor latency, the higher tumor incidence associated with 10<sup>4</sup> spleen cells and a high 3-MC concentration probably depended on the immunogenicities of the induced tumors and was therefore consistent with an immunostimulation of oncogenesis. (17 refs.)

See also:

\*(Rev.): 78-0064, 78-0065, 78-0080, 78-0081, 78-0082, 78-0083, 78-0084, 78-0085, 78-0086, 78-0087, 78-0094.

\*(Chem.): 78-0124, 78-0133, 78-0148, 78-0190, 78-0220, 78-0284.

\*(Viral): 78-0304, 78-0307, 78-0311, 78-0312, 78-0321, 78-0323, 78-0324, 78-0325, 78-0330, 78-0331, 78-0333, 78-0335, 78-0336, 78-0346, 78-0347, 78-0352, 78-0353, 78-0354, 78-0359, 78-0360, 78-0368, 78-0386, 78-0399, 78-0404, 78-0416, 78-0418, 78-0420, 78-0422.

\*(Path): 78-0471, 78-0479, 78-0482, 78-0484, 78-0486, 78-0497, 78-0507, 78-0537, 78-0542, 78-0573.



## PATHOGENESIS

- 78-0454 **Endometrial Sarcoma: Lymphatic Spread Pattern.** (Eng) DiSaia, P. J. (Dept. Obstetrics and Gynecology, Univ. California at Irvine Medical Center, 101 City Drive, S., Orange, CA 92668); Morrow, C. P.; Boronow, R.; Creasman, W.; Mittelstaedt, L. *Am J Obstet Gynecol* 130(1): 104-105; 1978.

Preliminary pathologic findings are reported for 28 cases of endometrial sarcoma treated by standard total abdominal hysterectomy and bilateral salpingo-oophorectomy or modified radical hysterectomy. Although the disease appeared limited to the uterus, including the cervix, approx one-third of the patients had positive pelvic lymph nodes and/or positive aortic nodes. In every case of nodal involvement, the myometrial invasion was to the middle or outer third region. (2 refs.)

- 78-0455 **Clear Cell Adenocarcinoma of the Uterine Cervix: A Histological and Histochemical Study.** (Eng) Baird, P. J. (Dept. Pathology, King George V Memorial Hosp., Missenden Road, Camperdown, New South Wales 2050, Australia); Russell, P.; Laverty, C. R. *Pathology* 9(3): 257-262; 1977.

A mullerian clear cell adenocarcinoma of the uterine cervix developed in a 26-yr-old woman with no known in utero exposure to nonsteroid estrogens and no structural genital tract abnormalities. She had been on a combination contraceptive pill for 7 yr. This case is illustrative of the 30%-50% of mullerian tumor patients who have few if any associated cervical and vaginal abnormalities and no history of fetal exposure to nonsteroid estrogens. Other etiologic factors must be involved in these cases. (13 refs.)

- 78-0456 **Screening of Cervical Cytological Samples Using Coherent Optical Processing. Part 1.** (Eng) Pernick, B. (Grumman Aerospace Corporation, Bethpage, NY 11714); Kopp, R. E.; Lisa, J.; Mendelsohn, J.; Stone, H.; Wohlers, R. *Appl Optics* 17(1): 21-34; 1978.

A coherent optical data processing system for the cytological screening of Pap smears by cell image photographs is described. Two-dimensional Fourier spectra of normal and abnormal cells are presented, and several parameters that differentiate between the two are identified. This system appears practical in terms of the number of cells to be processed. A high-speed optical transducer would be required for processing large numbers of cells without photography in a reasonable time interval. (8 refs.)

- 78-0457 **Screening of Cervical Cytological Samples Using Coherent Optical Processing. Part 3.** (Eng) Pernick, B. (Grumman Aerospace Corporation, Bethpage, NY 11714); Jost, S.; Herold, R.; Kopp, R. E.; Mendelsohn, J.; Wohlers, R. *Appl Optics* 17(1): 43-51; 1978.

A modified Fourier spectrum analyzer system for screening cervical cytological (Pap) smears is described in which an optical transducer is used to contain the cell images. Cell discriminant features are obtained from the transform spectrum of the transducer-modulated image. The ability of this system to classify cells from feature measurements is comparable with cell-by-cell classification based on cell photography. Examples of how the transducer-stored images can be altered in a controlled manner and how discriminant features determined from these images can be used to augment the system's performance are presented. (4 refs.)

- 78-0458 **Screening of Cervical Cytological Samples Using Coherent Optical Processing. Part 2.** (Eng) Wohlers, R. (Grumman Aerospace Corp., Bethpage, NY 11714); Mendelsohn, J.; Kopp, R. E.; Pernick, B. J. *Appl Optics* 17(1): 35-42; 1977.

The analytical portions of a previously published coherent optical data processing system developed to process cervical cell images are related. Representative cell images modeled as two concentric circles in a rectangular field of view are used to describe radical spatial frequency profiles for normal and malignant cells. The weighted Fourier transform distribution,  $p^2/F(p)^2$ , was most effective in bringing out normal/malignant cell transform differences. The photographic variables of contrast and gamma are significant factors in the ability to discriminate between cells on the basis of features of the Fourier transform spectrum. Cell images, preprocessed to achieve high contrast ratio and high gamma values, enhanced differences in the Fourier spectrum between normal and malignant cell types. A high background density in regions of the field of view outside a cell image reduced the level of the aperture contribution and aided normal/malignant cell differentiation. (4 refs.)

- 78-0459 **Thirty-Year Follow-up of Breast Cancer Kindred (Meeting Abstract).** (Eng) Gardner, E. (Utah State Univ., Logan, UT). *Am J Hum Genet* 29(6): 45A; 1977. (no refs.)



**78-0460 Likelihood Analysis of Inheritance of Breast Cancer Predisposition in a Mormon Pedigree** (Meeting Abstract). (Eng) Hill, J. (Univ. Utah, Salt Lake City, UT); Skolnick, M.; Carmelli, D.; Gardner, E. *Am J Hum Genet* 29(6): 53A; 1977. (no refs.)

**78-0461 Tumour Stimulation by Anti-oestrogens.** (Eng) McIntosh, I. H. (Breast Unit, Royal Marsden Hosp., London, England); Thynne, G. S. *Br J Surg* 64(12): 900-901; 1977.

The case reports of a 48-yr-old woman with  $T_1N_0M_0$  carcinoma of the breast at presentation and a 34-yr-old woman with a  $T_1N_2$  breast carcinoma at presentation are presented. They were treated with antiestrogen agent tamoxifen and the antiprolactin agent bromocriptine, with progression of disease. In each patient, the progression occurred in the absence of ovarian and adrenal function. Both had regression of symptoms when the tamoxifen was removed, and both responded to immunochemotherapy. The reasons for this reaction to the antiestrogen is unknown. (13 refs.)

**78-0462 A Statistical Analysis of Breast Cancer Dissemination Routes Based on Autopsy Records.** (Jpn) Yamashita, N. (Dept. Radiology, Kanto Teishin Hosp., Japan). *Jpn J Cancer Clin* 23(13): 1206-1209; 1977.

A statistical analysis of the autopsy records of 502 patients with primary breast cancer showed that further cancer dissemination was influenced by the presence of metastases at three major sites: lungs, liver, and bones. The lung effect was the most important in that metastases in this organ were associated with the highest incidence of metastases at minor sites. (6 refs.)

**78-0463 Radioimmunoassay of Some Hormones Simultaneously Measured in Serum and Breast Cyst Fluid.** (Eng) Srivastava, L. S. (Metabolism Div., Internal Medicine, Room 5563, Coll. Medicine, Univ. Cincinnati, 231 Bethesda Ave., Cincinnati, OH 45267); Pescovitz, H.; Singh, R. D.; Perisutti, G.; Knowles, H. C. *Experientia* 33(12): 1659-1660; 1977.

Hormone concentrations in breast cyst fluid and serum samples obtained simultaneously were determined in 14 women presenting for cyst aspiration. There were no significant differences between cyst fluid and serum levels of prolactin and thyroid-stimulating hormone. However, both luteinizing hormone and follicle-stimulating hormone concentrations were higher in the serum than in the cyst fluid. Separate analyses were performed in four women with multiple cysts. Luteinizing hormone and prolactin levels varied from cyst to cyst in the same woman, but none of the differences were as marked

as those between serum and cyst fluid. These patients will be followed for a minimum of 10 yr to determine any correlation between these findings and breast cancer. (21 refs.)

**78-0464 Ovarian Cystoma and Ovulation, a Histogenetic Concept.** (Eng) Zajicek, J. (Cytology Dept., Inst. Tumour Pathology, Kaolinska Sjukhuset, Stockholm 60, Sweden). *Tumori* 63(5): 429-435; 1977.

The characteristics of three groups of tumors of the ovary and testis (germ cell tumors, sex cord stromal tumors, and epithelial tumors) are reviewed, and their relative frequencies illustrated by data extracted from the Swedish Cancer Registry for 1959-1965. The most common of the registered gonadal neoplasms were epithelial tumors of the ovary (cystomas), which do not occur in the testis. It is generally agreed that cystomas arise from inclusions of ovarian surface epithelium in the ovary. The nonoccurrence of cystomas in the testis has led to the hypothesis that epithelial inclusions arise during the reparative period following ovulation. This concept can account for the formation of cystomas in young women, for the general absence of cystomas before puberty, and for the decrease of benign cystomas after menopause. (14 refs.)

**78-0465 Comparative Morphological and Cytogenetical Investigations on Human Ovarian Granulosa Cell Tumors.** (Eng) Moraru, I. (Victor Babes Inst. Pathology Medical Genetics, Splaiul Independentei nr 99-101, sect 6, 76201 Bucharest 35, Rumania); Fadei, L. *Arch Geschwulstforsch* 47(6): 541-549; 1977.

Three ovarian granulosa cell tumors from patients aged 58, 46, and 54 yr were compared with regard to the morphological and cytogenetical stages of their progression. Two of the tumors were more differentiated and possessed microfollicular and macrofollicular patterns and Call-Exner bodies. The third tumor was less differentiated with sarcomatoid patterns prevailing. This less differentiated tumor also had a higher chromosome number (25% near tetraploid) and malignant triploid cell type occurrence. It is suggested that the first two tumors were premalignant while the last one (less differentiated) was malignant. (6 refs.)

**78-0466 The Origin and Clinical Behavior of the Parovarian Tumor.** (Eng) Genadry, R. (Dept. Gynecology and Obstetrics, Johns Hopkins Hosp., Baltimore, MD 21205); Parmley, T.; Woodruff, J. D. *Am J Obstet Gynecol* 129(8): 873-880; 1977.

A study of 132 benign parovarian cysts and 8 parovarian neoplasms demonstrated that most were of mesothelial (30% of the cysts) or paramesonephric origin (68% of the cysts and all the neoplasms). Four of the neoplasms were benign and four were low-grade papillary malignancies that arose in the broad ligament. Histologically, the latter resembled both tu-



bal and ovarian carcinomas. Multiple sections of the adjacent adnexa revealed no evidence of neoplastic or inflammatory abnormalities. Thus, papillary tumors can arise de novo from the pelvic mesothelium. (14 refs.)

- 78-0467 Comparison of Cancer Cell Surfaces of the Lower Reproductive Tract by Scanning Electron Microscopy.** (Eng) Sherman, A. I. (6767 W. Outer Drive, Detroit, MI 48235). *Am J Obstet Gynecol* 129(8): 893-908; 1977.

Cervical squamous cells simulate those of the vagina and vulva both histologically and by scanning electron microscopy. However, in areas of the cervix undergoing active metaplasia, there are cells that share some of the ultrastructural characteristics both squamous and columnar epithelium. In these cells, the presence of both cell types suggests gradual transition from columnar to squamous epithelium. Furthermore, the cells of severe dysplasia and of intraepithelial and invasive cervical squamous cancers of the cervix, although histologically similar to those of vaginal and vulvar cancers, are distinctly different when examined by scanning electron microscopy. These findings suggest that both metaplastic and neoplastic squamous cells are derived from the same progenitor columnar cells of the cervix, by orderly transition in the former and by atypical transformation in the latter. The distinctiveness from the vaginal and vulvar cells indicates different embryonic stem cell lines. (3 refs.)

- 78-0468 Benign Vaginal Rhabdomyoma.** (Eng) Gee, D. C. (Inst. Clinical Pathology and Medical Res., P.O. Box 108, Lidcombe, New South Wales 2141, Australia); Finckh, E. S. *Pathology* 9(3): 263-267; 1977.

The occurrence of a benign polypoid vaginal rhabdomyoma in a 52-yr-old woman is reported. Histologically, the tumor was characterized by large amounts of loose connective tissue, dilated thin-walled vascular spaces, and interlacing bands of striated muscle cells with prominent cross and longitudinal striations. Electron microscopy confirmed the origin from striated muscle. The pathogenesis of vaginal rhabdomyomas is possibly a localized area of abnormal mesenchymal differentiation. (12 refs.)

- 78-0469 Androgenesis as a Cause of Hydatidiform Mole.** (Eng) Wake, N. (Dept. Obstetrics and Gynecology, Asahikawa Medical Coll., Asahikawa, Japan); Takagi, N.; Sasaki, M. *J Natl Cancer Inst* 60(1): 51-57; 1978.

Chromosomal studies were performed on three molar products of conception and their parents, with particular attention being focused on pairs 3, 13, 14, 15, 21, and 22. In one case, both members of chromosome pairs 13 and 21 of the mole were traceable to the paternal 13 and 21 chromosomes, suggesting that the mole had only paternal sets of chromosomes. This result was also found in another case in which

no maternal chromosomes 3, 13, 15 or 22 were present, but a paternally derived pair 15 was. In the third mole, the absence of the maternal genome was inferred from the molar chromosomes 21, which was identified as being of paternal origin. Study of 10 metaphases from one mole after the incorporation of 150  $\mu\text{g/ml}$  5-bromodeoxyuridine indicated that regulatory mechanisms operate normally in moles. Thus, androgenesis apparently is causally related to the pathogenesis of complete hydatidiform moles. (16 refs.)

- 78-0470 Hepatic Adenoma and Oral Contraceptive Pills.** (Fre) Hureau, J. (Clinique thérapeutique chirurgicale, Hôpital de Vaugirard, 389, rue de Vaugirard, 75015 Paris, France); Benit, C.; Delavierre, P.; Bourdais, J. P. *J Clin Pathol (Paris)* 114(5): 339-350; 1977.

A 31-yr-old woman had a hepatic adenoma that was apparently related to 9 yr use of an oral contraceptive containing mestranol (Ovulen 28). The patient presented with fever, abdominal pain, hepatomegaly, and a palpable liver mass. The initial diagnosis was cholecystitis with an enlarged gallbladder. After hepatic arteriography, radioisotope scan with  $^{99\text{m}}\text{Tc}$ , and echotomography, the diagnosis was changed to a tumor of segment VI of the liver. The segment was removed, and histological examination of the tumor showed that it was an adenoma. There were multiple foci, the largest having a hemorrhagic center. The normal liver architecture had disappeared. Capillaries were dilated, there was hemorrhagic infiltration and abnormal fibrous strands, and areas adjacent to the adenomatous foci were characterized by dense collagen and networks of arterioles and venules. The foci were not encapsulated. (33 refs.)

- 78-0471 Serum  $\alpha$ -Fetoprotein in a Mouse Strain (C3H-AvylB) with Spontaneous Hepatocellular Carcinomas.** (Eng) Becker, F. F. (Dept. Pathology, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Stillman, D.; Sell, S. *Cancer Res* 37(3): 870-872; 1977.

The relationship between serum  $\alpha$ -fetoprotein (AFP) levels and spontaneous hepatocellular carcinoma was investigated in C3H-AvylB mice, which demonstrate a rapidly increasing incidence of hepatic cancer with age. Primary hepatocellular carcinomas developed in 16/57 of the males by age 8 mo and 12/23 by age 12 mo. In females, the incidence was 5/21 by age 12 mo. Although elevated AFP levels were associated with most of these tumors, no elevation of AFP was observed during the lifetime of the non-tumor bearers, despite their age-dependent risk for hepatic cancer. In the tumor-bearing mice there was no consistent relationship between serum AFP concentration and tumor size, type, or degree of invasion. Five of these mice did not demonstrate a significant elevation of circulating AFP compared to control mice. Therefore, whatever the age-related factors that lead to tumor formation in this mouse, they are not related to synthesis of significant amounts of AFP. (24 refs.)



**78-0472 Lymph Drainage from the Vulva and the Foot as Demonstrated by  $^{198}\text{Au}$ .** (Eng) Bartholdson, L. (Dept. Plastic Surgery, Sahlgrenska Sjukhuset, S-413 45 Gothenburg, Sweden); Hultborn, A.; Hulten, L.; Roos, B.; Rosencrantz, M.; Ahren, C. *Acta Radiol [Ther] (Stockh)* 16(3): 209-218; 1977.

Lymphatic drainage from the vulva and foot was investigated in seven women (26-70 yr old) with vulvar tumors (6 squamous cell carcinomas and 1 malignant melanoma). Forty-eight hours before surgery, a colloidal suspension of  $^{198}\text{Au}$  was injected sc into the center of the labia majora in five patients. In four of these, 38% Lipiodol Ultra Fluid was also injected intralymphatically into the dorsum of the foot 24 hr later (3 in the contralateral foot, 1 in the ipsilateral foot). In two patients,  $^{198}\text{Au}$  was injected sc in the dorsum of the foot only. Patients receiving  $^{198}\text{Au}$  injections in the central part of the labium majus had colloid in their bilateral inguinal and pelvic nodes.  $^{198}\text{Au}$  or Lipiodol injected in the foot could be detected in the ipsilateral inguinal and pelvic nodes. In one case, tracer was situated in nodes on both sides of the midline following lumbar node removal, indicating crossover only above the level of the pelvis. Thus, bilateral inguinal and low pelvic lymphadenectomy is logical in the treatment of carcinoma of the vulva; there is no need for contralateral lymphadenectomy in malignancies on the dorsum of the foot. (24 refs.)

**78-0473 Pathogenetic Examination of Prostatic Hyperplasia in Normal and Adenomatous Glands of Humans and Dogs:  $3\alpha$ -Reduction of Dehydrotestosterone.** (Ger) Jacobi, G. H. (Urologische Universitätsklinik, Langenbeckstrasse 1, D-6500 Mainz, W. Germany). *Endokrinologie* 70(2): 158-168; 1977.

The formation of  $3\alpha$ - and  $3\beta$ -androstanediol was examined in the cytosol fraction and microsomes of human and canine prostates. The 3-ketoreduction of dihydrotestosterone was assessed in 23 normal and 17 hyperplastic human glands with an av wt of 19 and 53 g, respectively, and in 23 normal and 28 hyperplastic canine prostates with wts ranging from 0.8 to 36 g. Eight dogs had developed benign prostatic hyperplasia spontaneously; in 20 dogs, the condition was induced by 1 to 6 mo treatment with androstanediol. Both androstanediols were detected in the microsomes and cytosol; NADH and NADPH were effective as cofactors in the reduction reactions. In human glands,  $3\alpha$ -androstanediol formation was significantly higher in adenomatous tissue, particularly the hyperplastic components, than in normal tissue. Androstanediol synthesis was 70 times greater in canine tissue than in human tissue. When prostate wts reached 14-16 g, there was a dramatic increase of  $3\alpha$ -androstanediol synthesis in the cytosol fraction, suggesting a change to unregulated growth.  $3\alpha$ -Androstanediol formation in the microsomes increased linearly; rates in prostates > 15 g were about 18 times higher than those in prostates < 5 g. Increased androstanediol formation might be involved in the pathogenesis of benign prostatic hyperplasia. (22 refs.)

**78-0474 Embryonal Carcinoma of the Testis in Elderly Men.** (Eng) Tuttle, J. P. (Dept. Urology, Medical Univ. South Carolina, Charleston, SC 29403); Pratt-Thomas, H. R.; Thomason, W. B. *J Urol* 118(6): 1070-1072; 1977.

The case report of a 96-yr-old black man with an embryonal carcinoma of the testis is presented. Histological examination failed to reveal any differentiation along intra- or extraembryonic lines. In a review of 137 testicular tumors in patients >60 yr, 59 were of germ cell origin, and there were no embryonal carcinomas. This case represents the only pure embryonal carcinoma reported in the literature in men  $\geq$  60 yr and the oldest man with a testicular tumor. (10 refs.)

**78-0475 Multicellular Origin of Parathyroid "Adenomas" (Letters to Editor).** (Eng) Gown, A. M. (Univ. Washington, Seattle, WA 98195); Fialkow, P. J.; Jackson, C. E.; Block, M. A.; Greenwald, K. A. *N Engl J Med* 298(1): 53-54; 1978.

A previous study indicating that parathyroid hyperplasias and adenomas may be similar biologically on the basis of glucose-6-phosphate dehydrogenase isoenzyme analysis fails to take into account contaminant that may distort the enzyme ratio. In a rebuttal, it is stated that it would take at least a 50% nonneoplastic cell admixture in the tumor to distort the ratio. Actual contamination is believed to be < 15%. (9 refs.)

**78-0476 A Morphometric Study of Nuclei, Nucleoli and Nuclear Bodies in Goitres and Papillary Thyroid Carcinomas.** (Eng) Sobrinho-Simoes, M. A. (Lab. Pathology, Oporto Medical Sch., Oporto, Portugal); Goncalves, V.; Sousa-Le, F.; Cardoso, V. *Experientia* 33(12): 1642-1643; 1977.

Morphometric examinations were performed on the nuclei, nucleoli, and nuclear bodies of 4 patients with diffuse hyperplastic goiters (I), 3 patients with papillary carcinoma of the thyroid (II), and 6 patients with occult sclerosing carcinomas of the thyroid (III). There was a significant correlation between the surface-to-volume ratios of Groups II and III. Other significant correlations were found between the volumetric density of the nucleoli and that of the nuclear bodies between Groups I and II and between Groups I and III, the number of complex nuclear bodies between I and II, and the number of complex nuclear bodies per unit area of the nuclear profile between both I and II and I and III. These findings indicate an increased nucleolar activity in papillary thyroid carcinomas, but they do not rule out a disturbed RNA metabolism in their pathogenesis. (12 refs.)



- 78-0477 Hereditary Multiple Fibrofolliculomas with Trichodiscomas and Acrochordons.** (Eng) Birt, A. R. (714-233 Kennedy St., Winnipeg, Manitoba R3C 3J5, Canada); Hogg, G. R.; Dube, W. J. *Arch Dermatol* 113(12): 1674-1677; 1977.

Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons were studied in a kindred of 70 persons because six members of a sibship of 9 in the kindred had hereditary medullary carcinoma. Two siblings with thyroid neoplasms and two without had numerous small papular skin lesions. This kindred had become the repository of two different hereditary afflictions: the carcinoma had been inherited through a male antecedent and the multiple skin hamartomas through his wife. Forty members of the kindred were examined and reliable histories regarding the presence of skin lesions were obtained for the remaining 30. Thirty-seven members were >25 yr. Fifteen of them had fibrofolliculomas that had been inherited as an autosomal dominant trait and had acrochordon-like papillomas intermingled with the other lesions. None of the 33 members < 25 yr had the small-dome shaped tumors, acrochordons, disseminated neurofibromatosis, tuberous sclerosis, Cowden's multiple hamartoma syndrome or mucosal neuromas. The small skin tumors were classified as fibrofolliculomas. The pathology of the lesions is presented. (11 refs.)

- 78-0478 Pituitary Microadenomas in Relation to Gynecologic Disease (Letter to Editor).** (Eng) Chez, R. A. (Dept. Obstetrics and Gynecology, Howard Univ. Coll. Medicine, Washington, DC 20060). *Am J Obstet Gynecol* 129(8): 929; 1977.

In studies of the role of pituitary microadenomas in gynecologic disease, the incidence of these tumors in the general population will have to be considered. Of 1,000 patients (age range 2-86 yr) autopsied for causes of death not related to clinical pituitary dysfunction, microadenomas were detected in 22.5%, mostly patients in the third to sixth decades. (3 refs.)

- 78-0479 An Anatomic-pathological Study of the Lymphoid System in Hamsters During the Growth of an SV40-induced Tumour.** (Eng) Loisiller, F. (Laboratoire d'Anatomie Pathologique des Services Communs de CNRS, B.P. no. 8, Villejuif, France); Zuinghedau, J.; de Vaux Saint Cyr, C. *Br J Exp Pathol* 58(5): 533-540; 1977.

The lymphoid organs of Syrian hamsters were studied following inoculation of the animals with  $10^3$  TSV<sub>1</sub>Cl<sub>2</sub> or TSV<sub>11</sub> cells, lines that had been transformed by simian virus 40 (SV40). Four phases of tumor growth were characterized by tumor wt: induction (up to 500 mg), second (up to 5.0 g), third (up to 20 g), and terminal (20 g). During induction, a

peritumoral plasma cell reaction was evident, the thymus had a large number of cells of epithelial origin at the periphery, the lymphoid follicles of the spleen were engorged, and the draining node had plasma cells at the corticomedullary junction. During the second phase, the peritumoral reaction increased, with penetration of plasma cells into the tumor, hyperplasia of the thymus and spleen continued, and there was no change in the nodes. During the third phase, the peritumoral reaction disappeared, the medullary area of the thymus was replaced by proliferating lymphoid cells, the spaces of the spleen had reduced numbers of lymphoid cells, and the peripheral regions of the follicles showed decreased cellularity and reduced plasmacytelike cells. The nodes were similar to those in the previous stages. During the terminal phase, there was no peritumoral reaction, epithelial cells disappeared from the spleen, and about 5% of the normal complement remained. The splenic reticulum was characterized by a small number of disseminated neoplastic cells, proliferation of lymphoblasts, and an increase in hematopoiesis. Plasmacytes were observed at the corticomedullary junction of all nodes studied; two showed evidence of tumor metastases. (15 refs.)

- 78-0480 Connubial Lymphoproliferative Malignancies: A Report of Nine Couples.** (Eng) Stephens, L. (Dept. Medicine, Div. Clinical Oncology, Kansas Univ. Medical Center, 39th St. at Rainbow Boulevard, Kansas City, KS 66103); Larsen, W. E.; Holmes, F. F.; Clark, G. M. *M Modiatr Oncol* 3(4): 351-358; 1977.

A report is presented of nine married couples, all > 40-yr-old and all with lymphoproliferative malignancies. The second partner developed cancer 0-18 yr after the first. Statistical analysis indicated that this association could have been due to chance alone, but the actual computation is difficult because of multiple referral centers. Similar reports from the literature are reviewed. (20 refs.)

- 78-0481 Multiple Myeloma in a Husband and Wife (Letter to Editor).** (Eng) Kardinal, C. G. (E. Fischel State Cancer Hosp. and Cancer Res. Center, Columbia, MO). *JAMA* 239(1): 22-23; 1978.

The fifth known occurrence of malignant melanoma in a husband and wife is reported. The electrophoretic mobility of serum myeloma proteins differed in this couple, and the husband, but not the wife, developed terminal plasma cell leukemia. (3 refs.)

- 78-0482 Familial Immunopathies: Report of Nine Families and Survey of Literature.** (Eng) Zawadzki, Z. A. (Div. Clinical Immunology and Oncology, Memorial Hosp., Prospect St., Pawtucket, RI 02860); Aizawa, Y.; Kikuchi, M. A.; Haradin, A. R.; Fisher, B. *Cancer* 40(5): 2094-2101; 1977.



nineteen individuals representing 9 familial instances of various immunopathies are reported. Multiple myeloma was diagnosed in 10 members of 5 families, lanthanic (idiopathic) paraproteinemia in 5 members of 2 families, and myeloma with lanthanic paraproteinemia in 4 members of the remaining families. The disorders occurred in parents and children in 3 families among siblings in 3 families, and in first cousins in 3. Immunochemical studies revealed IG paraprotein in 9 cases; IA in 3; IMI in 3 subjects belonging to the same family;ence-Jones protein in 1 case; and biclonal paraproteinemia, IgG, plus IAL in 1. Three individual cases of lanthanic paraproteinemia, discovered in a prospective study of 76 relatives of subjects with immunopathies, suggest that there may be a higher frequency of immunopathies among family members than in the general population of comparable age. The published reports on familial paraproteinemias are reviewed. (67 refs.)

78-0483 **Multiple Myeloma and Oat Cell Carcinoma.** (Eng) Smith, A. G. (Dept. Haematology, Stobhill Hosp., Glasgow, Scotland); Cumming, R. L. *J Clin Pathol* 30(11): 1053-1055; 1977.

The case report of a 60-yr-old man with oat cell carcinoma and multiple myeloma is presented. The immune reaction to neoplastic disease may account for a developing myeloma, and the impaired immune surveillance from a developing myeloma may enable a carcinoma to develop. (6 refs.)

78-0484 **Malignant Lymphopathy in a Patient Suffering from Acute Disseminated Lupus Erythematosus.** (Fre) Betourne, C. (Service de Medecine Interne, Hopital Ambroise-Pare, 9, av. Charles-de-Gaulle, F 92100 Boulogne, France); Cassan, P.; Franc, B.; Bacri, J. L.; Levy, J. *Nouv Presse Med* 6(31): 2753-2756; 1977.

A 58-yr-old woman developed a malignant centrofollicular lymphoma 3 yr after initiation of corticosteroid treatment for acute disseminated lupus erythematosus. The case is compared to those previously reported in the literature. (25 refs.)

78-0485 **Histiocytic Lymphoma with Sclerosis Arising from a Nodular Lymphoma with a Special Stroma Reaction: An Ultrastructural Study.** (Eng) Katayama, T. (Univ. Massachusetts Sch. Medicine, 55 Lake Ave. North, Worcester, MA 01605); Ceccacci, L.; Valu, A. F.; Horne, E. *Cancer* 40(5): 2203-2208; 1977.

The case of a 48-yr-old man with histiocytic lymphoma with sclerosis (HLS) that evolved from a nodular lymphoma of the skin is reported. This evolution was suggested by the three

cell types revealed by electron microscopy of formalin-fixed tissue: small lymphocytes with cleaved nuclei, large lymphocytes with uncleaved nuclei, and mesenchymal cells bearing desmosomes or hemidesmosomes. The mesenchymal stroma cells also contained an increased amount of intercellular connective tissue consisting of normal and fibrous long-spacing collagen fibers. These cells appear to produce the fine compartmentalizing fibrosis characteristic of HLS. (14 refs.)

78-0486 **Lymphoma Cutis of Apparent B Cell Origin.** (Eng) Goldberg, J. (Dept. Medicine, Section Hematology Oncology, State Univ. New York, Upstate Medical Center, Syracuse, NY 13210); Davey, F. R.; Lowenstein, F.; Gottlieb, A. J. *Arch Pathol Lab Med* 102(1): 15-18; 1977.

A 60-yr-old man had a nodular, poorly differentiated lymphoma that involved the lymph nodes, spleen, and skin. Malignant cells isolated from the lymph nodes exhibited the IgM $\lambda$  marker characteristic of B lymphocytes. (23 refs.)

78-0487 **Kaposi's Sarcoma in Polar Eskimos.** (Eng) Mikkelsen, F. (Dept. Dermatology, Finseninstitutet, Strandboulevarden 49, DK-2100 Copenhagen O, Denmark); Nielsen, N. H.; Hansen, J. P. *Acta Derm Venereol (Stockh)* 57(6): 539-541; 1977.

The case reports of two Eskimo men (aged 58 and 61) who developed Kaposi's sarcoma are presented. Although these cases provide no new data on the etiology or histogenesis of the disease, they do indicate that it is more common outside Africa than the literature indicates. (17 refs.)

78-0488 **Frequency of Osteosarcoma Among First-Degree Relatives of St. Bernard Dogs.** (Eng) Bech-Nielsen, S. (Dept. Epidemiology and Community Health, Sch. Veterinary Medicine, Louisiana State Univ., Baton Rouge, LA 70803); Haskins, M. E.; Reif, J. S.; Brodey, R. S.; Patterson, D. F.; Spielman, R. *J Natl Cancer Inst* 60(2): 349-353; 1977.

Osteosarcomas (OS) were found in 6 of 148 first-degree relatives (parents, siblings, offspring) of 21 index St. Bernard dogs, but not in any of 110 first-degree relatives of 18 breed-, age-, and sex-matched controls. Analysis of a composite pedigree constructed from individual four-generation pedigrees showed that all 21 index dogs were related. The coefficient of relationship for this group was significantly higher than that for the control group. The av coefficient of inbreeding of the OS group was lower than that of the controls, but the difference was not significant. This suggests that the presence



of specific genes within certain family lines, and not inbreeding per se, influenced susceptibility to OS. Formal testing of specific genetic hypothesis was not possible, but examination of the pedigree excluded fully penetrant autosomal dominant and X-linked recessive inheritance. Other monogenic models or more complex models, perhaps involving an interaction between genetic and environmental factors, cannot be excluded, nor can vertical transmission of an infectious agent. (10 refs.)

**78-0489 Blood Dyscrasias and Childhood Tumors and Exposure to Chlorinated Hydrocarbon Pesticides.** (Eng) Infante, P. F. (Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH); Epstein, S. S. In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C.* Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; 51-74; 1977.

Case reports are presented for five children with neuroblastoma associated with pre- or postnatal exposure to chlordane and for six patients (age 9-37 yr) with aplastic anemia or acute leukemia associated with exposure to chlordane or heptachlor. The aplastic anemia cases are consistent with previous reports of associations between chlorinated hydrocarbon pesticides and blood dyscrasias. The leukemia cases are noteworthy in view of reports of acute leukemia developing in subjects with aplastic anemia. Although perinatal pesticide exposure has not been implicated in childhood tumors, animal studies support the possibility of a transplacental carcinogenesis by chlordane. Epidemiologic studies are needed to evaluate the short- and long-term risks associated with the occupational or household use of chlordane. (63 refs.)

**78-0490 Blood-Borne Tumor Emboli and Their Adherence to Vessel Walls.** (Eng) Warren, B. A. (Dept. Pathology, Univ. Western Ontario, London, Ontario, Canada); Chauvin, W. J.; Philips, J. In: *Cancer Invasion and Metastasis: Behavior Mechanisms and Therapy.* Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 185-197; 1977.

Scanning electron microscopy/light microscopy observations on blood-borne tumor emboli in a case of mammary adenocarcinoma with metastases are presented. Sections of lung observed by light microscopy revealed numerous small blood vessels that contained tumor emboli from the adenocarcinoma. A form of circulation around these partially adherent tumor emboli was evident in the arrangement of the RBC within the remaining lumen of the vessels. Scanning electron microscopy of 8- $\mu$ m sections of lung disclosed emboli within the vessels. In some regions of the lung there were small pulmonary arteries that contained a mixture of partially organized thrombus on which fibrin was deposited. It appeared that the peripheral branches of the main artery had been occluded by tumor emboli, and retrograde thrombosis had en-

sued. From these results and those of previously published studies, it appears that adhesion of the blood-borne tumor embolus to the vessel wall is influenced by three factors: (1) alteration in the coagulation cascade and in the blood procoagulant coat enveloping the tumor embolus and/or the adherent platelets; (2) alteration in the endothelial lining of the vessel wall; eg, damaged and/or regenerating endothelium or variation in endothelial structure in various organs; and (3) alteration in blood flow such as stasis of flow and impaction of embolus in the capillary bed. (20 refs.)

**78-0491 Transplantable Granulocytic Leukemia Strain 13 Guinea Pigs.** (Eng) Evans, W. (Lab. Biochemistry, NCI, NIH, Bethesda, MD 20001); Mage, M. G.; Hsu, C. K.; Himmelhoch, S. R.; Smith, G. *Cancer Res* 38(1): 130-136; 1978.

The general biological and histopathological characteristics of a granulocytic leukemia, now in its 13th transplant generation in strain 13/N guinea pigs, are reported. The guinea pig that developed the original granulocytic leukemia used for transplantation was among a group of 10 10-wk-old guinea pigs given N-nitroso-N-butylurea (BNU) in the drinking water at a concentration of 0.20% for 21 wk. This animal was the only one that developed leukemia during a 10-mo observation period after treatment with BNU was stopped. Transplantation of the original leukemia cell line was achieved by serial ip injections of leukemic blood marrow cells into normal 3- to 7-wk-old guinea pigs. Macroscopically and microscopically, this leukemia resembled the chronic myelogenous leukemia form in humans. Histochemical studies showed that, unlike the human leukemic cells, those in the leukemic guinea pigs were alkaline phosphatase-positive. Electron microscopy studies revealed numerous intracisternal A-type particles, which are not found in corresponding normal WBC. Whether these particles are related to the disease or simply endogenous coronaviruses concomitantly induced by the carcinogen is not known. (18 refs.)

**78-0492 Acute Granulocytic Leukemia Following Successful Treatment of Rhabdomyosarcoma.** (Eng) Hensley, M. F. (Dept. Pediatrics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Cangir, A.; Culbert, S. J.; van Eys, J. *Am J Dis Child* 131(12): 1417; 1977.

A 6.5-yr-old girl developed acute granulocytic leukemia after receiving 6,000 rads of radiotherapy, actinomycin D, vincristine, and cytoxan for alveolar rhabdomyosarcoma. It is suggested that the combination of chemotherapy with radiotherapy was responsible for the short latent period in this patient. (10 refs.)



- 78-0493 Cytodifferentiation in the Acute Myeloblastic Leukemias of Man.** (Eng) Lan, S. (Albert Einstein Coll. Medicine, Yeshiva Univ., Dept. Surgery, 1300 Morris Park Ave., Bronx, NY); McCulloch, E. A.; Till, J. E. *J Natl Cancer Inst* 60(2): 265-269; 1978.

A comparison study of leukemia and nonleukemia myelopoiesis is described in which correlation analysis of the numbers of colony-forming progenitor cells was used to quantitate the human pluripotent stem cells. Marrow specimens were obtained from 24 patients with untreated acute myeloblastic leukemia, 22 patients under treatment, and 29 patients with no hematologic malignant disease. Three classes of progenitor cells were assayed: burst-forming units dependent on erythropoietin (BFU-E), colony-forming units dependent on erythropoietin (CFU-E), and granulopoietic progenitors; ie, colony forming units dependent on colony-stimulating activity (CFU-C). For leukemia marrows at the time of diagnosis and during treatment and for nonleukemia marrows, the numbers of progenitor cells detectable by the three assays tended to be positively correlated with one another. However, no positive correlations were seen between marrow blasts and any of the three progenitor cell classes. Although the BFU-E showed significant positive correlations with most of the mature cell types during treatment, this was not so at diagnosis. Great patient-to-patient variation was found among all three groups of patients. Reasons for this are argued. If it is assumed that the positive correlations between progenitors reflect lineage relationships, then these results are compatible with a shared relationship of the colony-forming cells to a pluripotent cell of origin. (30 refs.)

- 78-0494 A Case of Chronic Myelogenous Leukemia with Atypical Clinical Course Seen in a Radiological Worker.** (Jpn) Sato, I. (Second Dept. Internal Medicine, Tohoku Univ. Sch. Medicine, Tohoku, Japan); Endo, K.; Mikami, M.; Niikawa, K.; Sasaki, T.; Ishida, S.; Suzuki, T.; Tazima, G.; Horino, Y.; Saeki, S.; Onodera, S.; Yoshinaga, K. *Jpn J Clin Hematol* 18(9): 1143-1149; 1977.

The case report of a 51-yr-old nurse with Philadelphia (Ph<sup>1</sup>) chromosome-positive chronic myelogenous leukemia is presented. She had a 22-yr history of unprotected occupational exposure to x-rays. The disease was first diagnosed upon a routine medical checkup, and at that time there was no splenomegaly, low neutrophil alkaline phosphatase level, confirmed Ph<sup>1</sup> chromosome, or marked neutrophilia. The disease followed an atypical course until death 15 mo later. (23 refs.)

- 78-0495 Non-random Chromosome Gains in Human Lymphoblastoid Cell Lines.** (Eng) Steel, C. M. (MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh, Scotland); Woodward, M. A.; Davidson, C.; Philipson, J.; Arthur, E. *Nature* 270(5635): 349-351; 1977.

Chromosome gain and loss was examined in 80 lymphoblastoid cell lines (55 without lymphoreticular malignancy, 17 with lymphoreticular malignancy, and 8 Burkitt's lymphoma lines) carrying Epstein-Barr virus. Based on an analysis of 36 lines, gains occurred much more frequently than losses. Absence of a chromosome was always associated with one or more unidentifiable abnormal chromosomes whose total length was at least equal to that of the missing chromosome; however, the Y chromosome was completely lost from two lines. Trisomy or partial trisomy occurred with remarkable frequency for chromosomes 3, 7, 8, 9, 12, and X + Y. Trisomy 7, which has been noted in several Burkitt's lymphoma patients, was found in 4/5 Burkitt's lines examined. However, trisomy 7 was not limited to Burkitt's derived lines. Trisomies 8 and 9 have been noted in acute nonlymphatic leukemia, polycythemia vera, and other myeloproliferative disorders. Trisomies 3 and 12 do not appear to be characteristic of any human neoplasm. (15 refs.)

- 78-0496 Carcinogen-induced Chromosome Breakage in Fanconi's Anaemia Heterozygous Cells.** (Eng) Auerbach, A. D. (Lab. Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Wolman, S. R. *Nature* 271(5640): 69-71; 1978.

Early passage skin fibroblasts from five patients were exposed to 0.01  $\mu$ g diepoxybutane (DEB) per millimeter of medium for 6 days and examined in an attempt to identify Fanconi's anemia (FA) heterozygous cell strain. There was approx a fivefold increase in chromosome breakage in the FA heterozygotes after DEB treatment, and the breakage fit a Poisson distribution. The aberrations observed in these cells were similar to those that occur spontaneously in FA homozygous cells, with open chromatid breaks being the most common finding. There was no increase in chromosome breakage in normal cells. These findings indicate that a clastogenic agent can be used in vitro to determine whether presumptive heterozygotes are gene carriers for FA. (17 refs.)

- 78-0497 The Relationship of Acquired Chromosomal Abnormalities to Malignancy and Autoimmunity in New Zealand Black Mice (Meeting Abstract).** (Eng) Friedman, J. M. (Univ. Washington, Seattle, WA 98105). *Diss Abstr Int [B]* 38(6): 2526-B; 1977. (no refs.)

- 78-0498 Evidence for Chromosomal Instability in Retinoblastoma Patients and Band Assignment of the Occasionally Associated Chromosome 13 Deletion (Meeting Abstract).** (Eng) Welch, J. P. (Dalhousie Univ., Halifax, Nova Scotia, Canada); Fiander, D. C.; Main, M. *Am J Hum Genet* 29(6): 113A; 1977. (no refs.)



- 78-0499 Specificity of the Deletion of Chromosome #15 in Mouse Plasmacytoma.** (Eng) Yoshida, M. C. (Chromosome Res. Unit, Faculty Science, Hokkaido Univ., Sapporo 060, Japan); Moriwaki, K.; Migita, S. *J Natl Cancer Inst* 60(1): 235-238; 1978.

Karyotypic analyses were performed of the 63-1 and NP-38-ABCD mouse plasmacytomas which originated in BALB/c mice. The latter was a subline of MSPC-1. In NP-38-ABCD, the modal chromosome number was 38, no intact #3 or 6 was observed, and the Y chromosome was absent. Two marker chromosomes, the elongated #12 and the deleted #15 were seen in virtually every cell examined. Chromosome constitution remained stable throughout the 3 yr study. The 63-1 tumor had a unimodal distribution of chromosome number, with a sharp peak at 43. However, two karyotypically distinct populations, a and b, were present in a ratio of 90:10. In the a population, #10 and 15 were present as a single copy/cell, and #6 was present in triplicate. No intact X chromosome was found and the Y was missing. A shortened #15 was consistently present with the missing segment probably inserted into #10. The only difference between a and b was that b had four copies of #6 and two copies of #15. It was postulated that the a population was derived from the b. The only common marker between 63-1 and NP-38-ABCD was the deletion of #15, suggesting that this is a tumor-specific marker chromosome in mouse plasmacytoma. (17 refs.)

- 78-0500 Pericentric Inversion of Chromosome 1: Frequency and Possible Association with Cancer.** (Eng) Atkin, N. B. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England); Baker, M. C. *Cytogenet Cell Genet* 19(2/3): 180-184; 1977.

The frequency of pericentric inversions of chromosome 1 was investigated in 76 patients with malignant disease and 68 controls. Six patients with C band heteromorphism had pericentric inversion; another six patients without the heteromorphism also had inversion. Among the controls, two patients with C-band heteromorphism and one without had pericentric inversion. The six patients who were positive for both were three patients with carcinoma of the ovary, one with seminoma, one with carcinoma of the breast, and one with lymphosarcoma. The six with inversion only represented four patients with carcinoma of the ovary and two with Hodgkin's disease. Determination of inversion and heteromorphism was not possible in 32 patients and 37 controls. Thus, a minimum of 15% of the cancer patients and 4% of the controls had inversion, suggesting that inversions may be relatively common in cancer patients. The findings are discussed. (10 refs.)

- 78-0501 Population Kinetics of Chromosomally Abnormal Human Fibroblast Subpopulations.** (Eng) Benn, P. A. (Dept. Human Genetics, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA 19174). *Cytogenet Cell Genet* 19(2/3): 136-145; 1977.

Chromosomally abnormal human fibroblast subpopulations were studied in clones derived from 5 normal individuals and 11 mineral oil workers. A total of 21 clones with 10% or more abnormal cells were identified at low passage levels. At high passage, the number of abnormal clones dropped to 11; the total number of cells with stable rearrangements declined from 280 to 164, but there was no significant change in frequency of cells with unstable rearrangements or gaps at breaks. Nineteen of the 21 abnormal clones showed a stable or declining frequency relative to the normal cells. Appearances of new clones was rare at higher passages; in the cell lines in which new clones were found, large numbers of abnormal clones had been present at lower passages. The selection against cells with rearrangements may reflect a property of chromosome organization that ensures that cytogenetic abnormalities do not normally accumulate in rapidly dividing cells. It is suggested that mutations would only cumulate in slowly growing or nondividing tissues and that mutations giving a growth advantage in rapidly dividing tissues could be important in malignant transformation. (refs.)

- 78-0502 Specific Break Points in Chromosomally Abnormal Human Fibroblast Subpopulations.** (Eng) Benn, P. A. (Dept. Human Genetics, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA 19174). *Cytogenet Cell Genet* 19(2/3): 118-135; 1977.

Chromosome break points were studied in 23 cultures derived from biopsy of normal individuals, workers exposed to mineral oil, and normal unexposed tissues of patients with severe sunlight-induced skin keratoses. Twenty-five chromosomally abnormal clones were identified in lines cultured in media of different compositions. In two lines derived from the same biopsy, an identical chromosome rearrangement was found. All abnormal karyotypes showed no major loss of chromosomal material. Of 81 break points identified, 31 appeared in the terminal bands; there was generally evidence of reciprocity in these exchanges. The deleted chromosomes appeared to be quite stable and there was particular specificity for terminal bands. Various rearrangements are described based on the assumption that the translocations were reciprocal. It was not possible to identify a single factor responsible for the abnormalities; the finding of two clones with identical karyotypes in independent lines from the same biopsy and a different clone in a third line suggests that some abnormal cells are present in vivo. The findings are discussed based on data from the literature. (refs.)

- 78-0503 Subpopulations of Cytogenetically Abnormal Cells in Fibroblast Cultures Derived from Workers Exposed to Mineral Oil.** (Eng) Benn, P. A. (Dept. Human Genetics, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA 19174); Harnden, D. G.; Fairburn, E. A. *J Natl Cancer Inst* 60(1): 45-50; 1978.



The frequency of abnormal fibroblast clones in skin biopsy specimens obtained from 10 patients who had been exposed occupationally to mineral oil was compared to that of control specimens taken from the same patient. The patients ranged in age from 45 to 76 yr old; control biopsies were generally taken from the upper arm, test biopsies from the hands and forearm. The total number of cells with recognizable chromosome rearrangements was significantly higher in lines grown from oil-exposed skin compared with control lines (121 cells had rearrangements vs 63 in controls). However, there was no evidence for increased numbers of different rearrangements in the exposed lines compared with controls. The frequency of gaps and breaks was similar in the two groups. Abnormal clones formed a greater proportion of the total cell population in the lines from the exposed tissue compared with control lines. This difference in clone size may be a result of the in vivo exposure to mineral oil or other environmental agents. (29 refs.)

**78-0504 Malignant Melanoma Metastases in the Placenta: A Case Report.** (Eng) Russell, P. (Dept. Pathology, King George V Memorial Hosp., Missenden Road, Camperdown, New South Wales 2050, Australia); Laverty, C. R. *Pathology* 9(3): 251-255; 1977.

Of the 20 previously reported cases of maternal malignancy metastasizing to the placenta and/or associated infant, 14 were of malignant melanoma. The present case of widespread maternal melanoma metastatic to the placenta further emphasizes this trend. The mother died 2 wk after induced labor at 36 wk gestation. The infant, despite fetal vascular invasion, is tumor-free at 5 mo postdelivery. (7 refs.)

**78-0505 Familial Melanoma in Three Generations (Meeting Abstract).** (Eng) McCaw, B. K. (Univ. Oregon Health Sciences Center, Portland, OR); King, C. R. *Am J Hum Genet* 29(6): 71A; 1977. (no refs.)

**78-0506 Connections between Pigment Loss and Melanomatosis in Gray Horses of the Lipizzaner Breed (Meeting Abstract).** (Eng) Gebhart, W. (Univ. Vienna, Vienna, Austria); Niebauer, G. *Yale J Biol Med* 50(5): 45; 1977. (no refs.)

**78-0507 Cutaneous Tumors in Sun-exposed Areas Following Renal Transplantation (Meeting Abstract).** (Eng) Conant, M. A. (No affiliation given); Naversen, J. N.; Epstein, E.; Goodman, R.; Epstein, J.; Farber, E.; Field, L.; Epstein, E., Sr. *Arch Dermatol* 113(12): 1738; 1977. 3 refs.)

**78-0508 Eight Years of Gardner's Syndrome in One Family.** (Ger) Feurle, G. E. (Medizinische Universitäts-Poliklinik, 6900 Heidelberg 1, Hospitalstrasse 3, W. Germany); Baldauf, G.; Hopker, A. *Dtsch Med Wochenschr* 102(46): 1678-1683; 1977.

All affected members of a family with Gardner's syndrome exhibited the triad of skin tumors, osteomas, and polyps of the colon since 1968. Although the osteomas developed during puberty and remained constant thereafter and no new skin tumors appeared after puberty, most colonic polyps occurred in adolescence or thereafter. Malignant transformation occurred after an interval of several years. (33 refs.)

**78-0509 Cervical Thorotrast Granuloma: An Iatrogenic Cause of Dysphagia.** (Eng) Burrell, M. (Dept. Diagnostic Radiology, Yale-New Haven Hosp., 333 Cedar St., New Haven, CT 06510). *Gastrointest Radiol* 2(3): 293-295; 1977.

A Thorotrast (thorium dioxide) granuloma of the neck was diagnosed in a 59-yr-old man who presented with dysphagia 27 yr after undergoing carotid arteriography, in which Thorotrast was the contrast medium used. The radiographic and histopathologic findings are summarized. (13 refs.)

**78-0510 Mesothelioma Possibly due to Environmental Exposure to Asbestos in Childhood.** (Eng) Arul, K. J. (Dept. Pathology, Royal Berkshire Hosp., Reading RG6 2AD, England); Holt, P. F. *Int Arch Occup Environ Health* 40(2): 141-143; 1977.

A 43-yr-old woman was diagnosed as having diffuse pleural mesothelioma with numerous metastases. Two years of her childhood had been spent in the vicinity of an asbestos factory, which deposited a white dust on nearby houses. It is suggested that the asbestos exposure was the cause of the tumor. (6 refs.)

**78-0511 Effect of Cyclophosphamide and Other Drugs on Artificial Pulmonary Metastases in Mice.** (Eng) Brown, J. M. (Dept. Radiology, Stanford University Medical Center, Stanford, CA 94305). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 411-413; 1977.

Pulmonary metastases were evaluated in C3H mice inoculated ip with cyclophosphamide (CP), actinomycin D, or mitomycin 24 hr prior to sc injection of syngeneic KHT sarcoma cells. CP enhanced lung colony formation by a factor of 100, whereas the other two drugs caused only a slight



enhancement. The enhancing effect of 100 mg/kg CP persisted for up to 1 wk, but a second 100-mg/kg dose did not interact with the first to give an effect comparable to that produced by a single 200-mg/kg dose unless < 24 hr separated the doses. Preliminary light and electron microscope studies suggested that the CP effect was due to a more rapid migration of tumor cells from the capillaries to the alveoli. (2 refs.)

**78-0512 Kinetics of Metastasis in Experimental Tumors.**

(Eng) Simpson-Herren, L. (Southern Res. Inst., Birmingham, AL 35205); Springer, T. A.; Sanford, A. H.; Holmquist, J. P. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 117-133; 1977.

Growth kinetics were studied in the Lewis lung carcinoma (3LL)-BDF<sub>1</sub> murine system. Sc-implanted 3LL was characterized by an increase in mass doubling time and an increase in length of the cell cycle (Tc) from 17 hr at day 5 to 25 hr at day 21. The thymidine index (TI) decreased with increasing tumor mass from about 0.50 at 350 mg to < 0.30 at 4,000 mg. Lung metastases (LM) were established in all mice by day 6. The Tc was shorter (14 hr at day 21) and the TI significantly higher in the LM than in the primary at any point in time when both could be studied. The presence of a large growing tumor suppressed the TI of the LM and increased the life span of the mice. A growing primary or LM had little effect on the growth of artificial brain metastases. However, small foci of 3LL cells in the brain had a mean pulse TI (approx 0.55) that equaled the max value observed for LL3 under any conditions examined. Excision of the primary increased the TI of the residual LM for 10-14 days and had a slight but consistent adverse effect on life span. Sham surgery also increased the TI of the LM and, to a lesser degree, of the primary for about 7 days. Grain-count distributions for the LM at 96 hr after excision or sham surgery indicated that more highly labeled cells are found in the excision than in the control (nonoperated) group, even though the length of the S phase is identical. A similar but less pronounced result occurred in the sham surgery group. By 14 days after surgery (day 28 postimplant), no mice survived in the sham group, but highly labeled cells were still present in the excision group. (31 refs.)

**78-0513 An Inhibitory Mechanism of Blood-borne Metastasis by Sulfated Polysaccharides.** (Eng)

Tsubura, E. (Third Dept. Internal Medicine, Sch. Medicine, Takushima Univ., Takushima, Japan); Yamashita, T.; Higuichi, Y. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 367-381; 1977.

The antimetastatic effect of sulfated polysaccharides on induced pulmonary metastasis was examined in female Wistar-Kyoto strain rats. The sulfated polysaccharides tested were xylan sulfate (XS), dextran sulfate (DS), chondroitin polysulfate (CPS), chondroitin sulfate (CSN), glucose polysulfate (GPS), sulfated alginic acid (Alg-S), agar sulfate (Aga-S), laminarin sulfate (LS), and mannan sulfate (MS). The inhibitory effect of these compounds were examined 2 wk after ip tumor injection. XS and DS (100 mg/kg) strongly inhibited the development of pulmonary metastasis; CPS was less inhibitory. CSN and GPS were not inhibitory. Alg-S, Aga-S, and MS (50 mg/kg) were moderately inhibitory. The antimetastatic activity of the sulfated polysaccharides correlated well with their anticoagulative activity. XS also increased the rate of disappearance of tumor cells from the lung, perhaps by impairing attachment to the endothelium of pulmonary lymphatic vessels. The inhibition of pulmonary metastatic nodules by XS was significant and approximately similar in each of the three types of ascites hepatomas (AH-109A, highly deformable cells; AH-30, moderately deformable; and AH-100B, slightly deformable) at 2 wk after tumor cell injection. AH-109A, survival rates between the treated and control groups were similar; with AH-130 and AH-100B, however, survival was prolonged markedly in the XS-treated rats. It is speculated that this difference in survival time is due to the differences in cell deformability of the three tumor strains. (65 refs.)

**78-0514 Some Observations on the Biology of Metastasis.** (Eng) Childs, J. N. (Chester Beatty Research Inst., Royal Cancer Hosp., Belmont, Sutton, Surrey, England).

In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 497-499; 1977.

Experiments aimed at detecting inapparent future metastases immediately after surgical removal of the primary tumor are briefly reviewed. A quantitative bioassay was used to detect residual tumor cells in the lungs postsurgery. Of 29 animals killed 7 days after excision of a primary leg tumor (HSBPA), none had gross lung metastases, but 6 were bioassay-positive for tumor cells in the lung. When animals that had borne HSBPA tumor for 14 days were treated 7 days after tumor excision with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), cyclophosphamide (CP) or whole-body irradiation, the number of residual tumor cells in the lung was affected by postoperative adjuvant therapy. With BCNU, 3/8 had bioassay-positive lungs with 1 postamputation node metastasis; CP, 0/8 developed postamputation metastases and 0/8 bioassay-positive; and with irradiation, 2/8 developed surgical metastases and 5/8 were bioassay-positive. In a preliminary experiment using the MC3 tumor, which grows from 10 cells ip, 0/8 rats had gross metastases at autopsy 7 days after excision but 4/8 had bioassay-positive lungs. These studies suggest that in tumors with a finite rate



metastatic occurrence, the ultimate growth or lack of growth of metastases depends on how low the number of tumor cells falls. Success in treating micrometastases will be related to reducing the numbers of tumor cells to a level at which they cannot grow. (8 refs.)

**78-0515 Metastasis in Pancreatic Duct Adenocarcinoma.** (Eng) Cubilla, A. L. (Dept. Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Fitzgerald, P. J. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 91-94; 1977.

The metastatic spread of pancreatic duct adenocarcinoma was investigated in 380 patients. Early routes could not be assessed, as 85% of the patients were discovered to have the disease when it had already spread beyond the pancreas. The sites most commonly involved were the liver (41%), peritoneum (25%), regional lymph nodes (20%), lung pleura (4%), lymph nodes, widespread (9%), skin (9%), cervix, vagina (8%), and bone (8%). The pancreas does not have a distinct capsule, which may explain the extensive retroperitoneal and peritoneal involvement. Venous involvement was conspicuous, and, presumably, this was the means by which the portal system was involved. The portal vein was also directly involved by retroperitoneal spread, resulting in occasional invasion of the vessel wall. The adjacent peripancreatic lymph nodes were usually invaded early. Upon autopsy, most patients had widespread metastases, but 4% died without metastases. Survival was related to lymph node involvement: patients with Stage I lesions survived twice as long as those with Stage II cancers. Nerve sheath invasion occurred in most cases, islet invasion in only a small percentage. In 50 patients, the presenting sign was the metastasis itself. The presenting site was the lymph nodes in 22; skin, 8; bone, 8; lungs, 4; liver, 3; cervix, vagina, 3; and brain, 2. Thirty-three of these patients had cancer of the body and tail of the pancreas, which are usually not as frequent as cancer of the head. The explosive burst of metastases seen in this cancer may indicate that a clone(s) of malignant cells that had acquired the ability to penetrate basement membranes or other boundaries became predominant in the cancer cell population, possibly with the aid of some extra organ factor favoring its growth. (17 refs.)

**78-0516 Benign Epithelial Nephroblastoma: A Contribution to Its Histogenesis.** (Eng) Stambolis, C. (Inst. Pathology, Univ. Essen, Hufelandstrasse 55, D-4300 Essen, W. Germany). *Virchows Arch [Pathol Anat]* 376(3): 267-272; 1977.

A 5-yr-old girl had a Wilms' tumor in her right kidney and a benign epithelial nephroblastoma in the opposite kidney. Both kidneys contained foci of well-differentiated blastema, and a direct relationship was demonstrated between the persistent nephrogenic tissue and the epithelial nephroblastoma. The latter may be the benign counterpart of the malignant Wilms' tumor. (7 refs.)

**78-0517 Arterial Embolization of Malignant Tumor: Report of Two Cases with Angiographic Findings.** (Eng) Stanley, P. (Dept. Radiology, Children's Hosp., Los Angeles, P.O. Box 54700, Los Angeles, CA 90054); Eto, R. *T. Radiology* 126(1): 93-94; 1977.

Two patients with arterial embolization of a malignant tumor are reported. The first was a 32-yr-old woman with an embolus from a renal adenocarcinoma in the common femoral artery. The second was a 12-yr-old boy with squamous cell metastases of a laryngeal and tracheal carcinoma in the posterior cerebral, common iliac, common femoral, and internal iliac arteries. Particular attention is placed on the radiological appearance of the emboli upon angiography. (10 refs.)

**78-0518 Needle Tract Seeding Following Aspiration of Renal Cell Carcinoma.** (Eng) Gibbons, R. P. (Section Urology, Virginia Mason Medical Center, Seattle, WA); Bush, W. H.; Burnett, L. L. *J Urol* 118(5): 965-967; 1977.

A 56-yr-old man with transitional cell carcinoma of the bladder and renal cell carcinoma had metastases along the needle tract 20 mo after an attempted needle aspiration of the latter. It is suggested that needle aspiration be reserved for patients in whom prebiopsy evidence indicates that the process is benign. (9 refs.)

**78-0519 Precursors of Human Gastric Cancer: Their Frequencies and Histological Characteristics.** (Eng) Nagayo, T. (Lab. Pathology, Aichi Cancer Center Res. Inst., Nagoya, Japan). In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 151-161; 1977.

Precancerous conditions and changes in human gastric mucosa are discussed. The former is a condition that is prone to become malignant or has a high risk of malignant transformation; the latter is a histological change directed toward the



development of cancer. Precancerous conditions include polyps, ulcers, and chronic gastritis. Hyperplastic polyps were only found in 0.6% of a cancer series, but adenomatous polyps were present in 69.2%. Thus, the latter carries a higher risk. About 75% of the early cancers (Type IIc) currently resected show changes of cancerous erosion; it is suggested that the decrease in Type III early cancer is due to a decrease in the number of chronic peptic ulcers. Precancerous chronic atrophic gastritis comprises focal atrophy, regeneration of the surface epithelia following erosion, cystic dilatation, or diffuse heterotopia of the gastric glands. Precancerous changes include maturation-arrested changes in atypical epithelia accompanied by irregular growth of the affected tubule or gland and focal aggregation of immature cells on the basal layer of the gastric mucosa. (5 refs.)

- 78-0520 A Study of the Morphology and Kinetics of Epithelial Migration in Response to Gastrointestinal Ulceration: A New Approach to the Cancer-Ulcer Question.** (Eng) Stemmermann, G. N. (Dept. Pathology, Kuakini Medical Center, Honolulu, HI); Hayashi, T.; Taki, M. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 37-47; 1977.

The morphology and kinetics of the reepithelialization of gastric ulcers were studied in cultures of mucosa from the pyloric antrum of gastrectomy specimens. Epithelial cells began to cover the ends of the muscularis mucosa by 6 hr of culture; neoeptithelialization observations indicated that the neoeptithelial layer was not uniform: it contained a random distribution of cells at different levels of maturation. Cell replication was suppressed among these cells, and they resembled cells in the upper portions of a gastrointestinal gland. A comparative in vivo and in vitro study was performed with male Wistar rats in which ulcers were produced by removal of a fragment of antral and intestinal mucosa. These fragments were used for organ cultures. Initial findings with both systems were the same, but after 48 hr, in vitro discrepancies resulted in the discontinuation of observation. Quantitative analyses of longer observation periods were limited to the in vivo system. In vivo studies up to 48 hr indicated that the neoeptithelium from both the rectum and antrum contained fewer labeled cells and fewer mitoses than the normal mucosa from these sites. Glands at the ulcer margins appeared to show more numerous labeled cells than the normal mucosa. Mitotic activity was not observed in the neoeptithelial layer until 48 hr after creation of the ulcer. Thus, if cancer induction at the moment of exposure to a carcinogen is related positively to the number of S-phase cells in the epithelium, migrant epithelium covering the ulcer would be at minimal risk but the epithelium at the margins of the defect would be at increased risk. (13 refs.)

- 78-0521 High Gastric Cancer Prevalence in San Marino: Familial Factors (Meeting Abstract).** (En) Jackson, C. E. (Henry Ford Hosp., Detroit, MI); Brownle, R. W.; Schuman, B. M.; Micheloni, F.; Ghironzi, G. *Am Hum Genet* 29(6): 58A; 1977. (no refs.)

- 78-0522 Five Cases of Lipoma of the Stomach, with Special Reference to Three Cases Accompanied by Gastric Carcinoma.** (Jpn) Tanaka, S. (2nd Dept. Pathology, Faculty Medicine, Kagoshima Univ., Kagoshima, Japan); Tokunaga, M.; Fukuda, M.M. *Jpn J Cancer Clin* 23(13): 1263-1266; 1977.

The occurrence of gastric lipomas in two women aged 46 and 73 yr and in three men aged 72-77 yr is reported. In three of the patients, the lipoma coexisted with a gastric adenocarcinoma. (11 refs.)

- 78-0523 The Significance of Villous Component in Colonic Polyps.** (Eng) Appel, M.F. (6624 Fannin, Houston, TX 77030); Spjut, H. J.; Estrada, R. G. *Am J Surg* 134: 770-771; 1977.

A total of 801 polyps from 611 patients were studied histologically. There were no malignant changes in any of the 25 pure adenomatous polyps, but 5 of them with up to 5% villous elements had carcinoma in situ (CIS). Of 304 villous polyps, there were 8 CIS's and 7 invasive cancers. Of 12 villous adenomas, there were 7 CIS's and 10 invasive cancers. None of the 124 hyperplastic polyps were malignant. Polyps with large amounts of villous elements were most likely to have malignant change. (9 refs.)

- 78-0524 The Evolution of Human Colon Cancer: Its Histological and Clinical Aspects.** (Eng) Muto, T. (Dept. Surgery, Sch. Medicine, Univ. Tokyo, Tokyo, Japan); Kamiya, J. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 335-350; 1977.

Histological and clinical evidence from several Japanese (J) and English (E) hospitals supporting the relationship between adenoma and cancer of the large bowel are presented. Based on 171 malignant tumors from one J hospital, 278 from an E hospital, and a review of the literature, it is suggested that at least 50% of all large bowel cancers arise from previously benign adenomas. A total of 142/145 cancers from an E hospital had a focus of cancerous tissue circumscribed by benign adenomatous tissue, suggesting that almost all cancers arise



from benign adenomas. Factors influencing the malignant potential of adenomas were studied in 299 tumors at a J hospital and 2,506 tumors at an E hospital. Malignant potential increased with size (cancer in adenomas < 1 cm was rare), villous adenomas had a greater malignant potential than other adenomas, and malignant potential increased with epithelial atypia. Furthermore, the larger the tumor, the more atypia and the greater the malignant potential. These findings held for both E and J patients. Although the evolution of adenoma-cancer of the large bowel is generally slow, it may be rapid in some cases, and there are examples of cancer in an adenoma < 1 cm. Specimens from patients with familial polyposis have a higher frequency of transformation than previously suspected. The role of small focal cancer in the adenoma-cancer sequence is discussed. It is suggested that the cancer involving from a small focal cancer may be diagnosed erroneously as de novo cancer. (32 refs.)

**78-0525 The Pathogenesis of Hyperplastic Polyps of the Colon: Ultrastructure and In Vitro Cell Kinetics.** (Eng) Hayashi, T. (Kuakini Medical Center, Honolulu, HI); Stemmermann, G. N.; Yatani, R.; Apostol, J. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan). 441 pp; 323-333; 1977.*

The pathogenesis of hyperplastic polyps was studied by transmission electron microscopy and in vitro organ culture followed by autoradiography using 15 colons removed for carcinoma, 3 for polyps, and 1 for diverticulitis. The earliest hyperplastic change is an elongation and minimal serration of the surface epithelium; the crypt architecture remains unchanged. The demarcations between the crypts, transitional zone and free surface of the mucosa are indistinct. Microvilli are frequent, tall, and associated with clavate fimbriae. Autoradiography revealed that the labeled zone of normal mucosa and hyperplastic polyps increases with continuous labeling and culture time, but the increase in the percentage of labeled cells in normal mucosa is greater than that of hyperplastic polyps. Thus the pattern of cell replication and migration in hyperplastic polyps is similar to that of normal mucosa, but there is a delayed exfoliation of surface epithelial cells in the polyps. The crypt columns become elongated and new cells become piled up because of retarded migration. It is suggested that hyperplastic polyps be called hypermaturation polyps. This concept explains the occasional finding of adenomatous changes in the superficial portions of the crypts and hyperplastic changes deeper in the crypt. The hypermaturation and functioning cells may facilitate absorption of carcinogens, predisposing these polyps to neoplastic change. The reason for the delayed exfoliation of the surface cells is unknown. (18 refs.)

**78-0526 Polyps of the Colon and Their Relationship to Carcinoma.** (Fl) Gulbis, A. (Ziekenhuis Deuyl, Ukel, Belgium); Ponette, S.; Demaeseneer, R. *Nederlandsche Maatschappij Geneeskunde 20(3): 163-178; 1977.*

A review of the literature and a study of 163 colon polyps removed from 107 patients indicated that the malignant evolution of a polyp depends mainly on its histologic structure. Villous polyps degenerate more frequently than adenomatous polyps, although the latter can undergo direct transformation or develop villous areas that subsequently degenerate. The risk of malignancy is high when multiple polyps are present. Since polyps are infrequent after age 80, their growth and transformation could be age-dependent. The incidence of both benign and malignant polyps is highest in persons aged 50-80 yr. (27 refs.)

**78-0527 Hereditary Adenomatosis of the Colon and Rectum: A Model of Tumor Progression.** (Eng) Kopelovich, L. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy.* Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp; 383-395; 1977.

Experiments on the growth characteristics of human skin fibroblasts (SF) from individuals with hereditary adenomatosis of the colon and rectum (ACR) are summarized. Phenotypic expressions that had previously been attributed to chemical or viral transformation by mammalian cells in vitro occurred in the cultured SF, presumably as a result of a germinal mutation. This mutation effected the expression of several growth abnormalities within normal-appearing SF from ACR genotypes. They included loss of contact inhibition, low serum requirement, elevated levels of plasminogen activator, redistribution of actin matrices, and increased susceptibility to transformation by an RNA oncogenic virus, but not loss of anchorage ability or the ability to form tumors in athymic mice. Anchorage independence was not present in ACR cells prior to transformation by Kirsten murine sarcoma virus (KiMSV). The results suggest that transformation of ACR cells by KiMSV had been facilitated to a large degree by a germinal mutation. Although no causal relationship could be clearly established, it is conceivable that cell transformation in situ is a temporal multistage process similar to that seen in cell cultures transformed in vitro. Identification of the phenotypic expressions associated with oncogenesis may facilitate their use as diagnostic indices for detecting latent forms of colon cancer in man. (49 refs.)

**78-0528 Hereditary Proximal Colonic Cancer.** (Eng) Lynch, P. M. (Dept. Preventive Medicine, Creighton Univ. Sch. Medicine, 2500 California St., Omaha, NB 68178); Lynch, H. T.; Harris, R. E. *Dis Colon Rectum* 20(8): 661-668; 1977.

The occurrence of colonic cancer (CC) in 10 families prone to adenocarcinoma of the colon was investigated. These families manifest hereditary syndromes that differ from familial



adenomatous polyposis coli in that none of the CC patients have evidenced multiple polyposis of the colon. There were 111 cases of anatomic site-documented CC in the 10 families. The mean age at onset was only 45 yr. The frequency of proximal CC in the families (64.3%) differed significantly from that in the general population ( $< 35\%$ ). Of the 59 men with CC, 24 had at least one extraprimarily malignancy of the colon or another anatomic site. Of the 52 women with CC and the 39 with endometrial cancer (since 9/10 families manifested the cancer family syndrome, these cancers were included here), 35 had at least one other primary cancer. The frequencies of multiple primary cancers were much higher than those in the general population (40% vs 2%-5%). Family members with proximal CC or endometrial cancer survived significantly longer than family members with distal colonic or rectal cancers. These results agree with the findings for 11 similar families from the literature and strongly suggest the existence of a heritable form of CC in which the proximal colon is at particularly high risk. (26 refs.)

- 78-0529 **Colonic Carcinoma in a Married Couple (Letter to Editor).** (Eng) Law, I. P. (Womack Army Hosp., Fort Bragg, NC 28307); Larson, A. *N Engl J Med* 297(24): 1353-1354; 1977.

The case report of a 60-yr-old woman who developed Duke 'C' carcinoma of the colon 1 yr after her 60-yr-old husband developed Duke 'B' carcinoma of the colon is presented. The couple had been married over 30 yr and had no consanguinity or unusual dietary habits. Some unknown environmental factor or genetic trait may have made them more susceptible to cancer. (1 ref.)

- 78-0530 **Pathological and Genetic Considerations of Colonic Manifestations of Adenomatosis Coli (Meeting Abstract).** (Eng) Utsunoyima, J. (Second Dept. Surgery, Polyposis Center, Tokyo Medical and Dental Univ., Tokyo, Japan); Iwama, T. *Gastroenterol Jpn* 12(4): 330; 1977. (no refs.)

- 78-0531 **Multiple Carcinomas of the Large Bowel: A Natural Experiment in Etiology and Pathogenesis.** (Eng) Enker, W. E. (Dept. Surgery, Univ. Chicago Pritzker Sch. Medicine, Chicago, IL); Dragacevic, S. *Ann Surg* 187(1): 8-11; 1978.

The follow-up data on 121 patients with multiple carcinomas of the large bowel are presented. Two groups of patients could be identified: (1) 68 (46 men, 22 women, aged 51-80 yr) with synchronous lesions and (2) 53 (31 men, 22 women)

with metachronous lesions. In Group 1, 4 had chronic ulcerative colitis, 13 benign colonic adenomas, and 11 malignant neoplasms unrelated to the large bowel. In Group 2, 3 had ulcerative colitis, 16 benign colonic adenomas, and 9 malignant tumors unrelated to the large bowel. In Group 2, the incidence of left-sided second primary lesions was higher than that of right-sided second primary tumors. Furthermore, the incidence of left-sided second primary tumors after right hemicolectomy was higher than the original incidence of left-sided lesions alone (77% vs 60%). Since dietary habits were assumed not to have changed much following surgery, it was concluded that bile acids may act as promoters of the second primary tumors. Follow-up studies also revealed that the second primary tumors are often in an asymptomatic, but advanced stage at detection. Subtotal colectomy is recommended for patients with synchronous or second metachronous malignant tumors. (8 refs.)

- 78-0532 **Proliferative Changes in the Epithelium of Human Lithiasic Gallbladder.** (Eng) Putz, G. (Gastroenterological Res. Unit, Vrije Universiteit Brussel, Rue Haute, 322, B. 1000, Brussels, Belgium); Willems, C. *Natl Cancer Inst* 60(2): 283-287; 1978.

The proliferative characteristics of normal (N) and lithiasic (L) human gallbladder epithelium were investigated. Specimens from nine patients with chronic symptomatic cholelithiasis and from nine L gallbladders were studied. Cellular DNA synthesis was observed by histoautoradiography after in vitro incubation of the specimens with  $^3\text{H}$ -thymidine. In the N gallbladders, the labeling index was low (0%-0.44%, mean 0.14%) and mitotic figures were rare (mean mitotic index, 0%). Of 20,701 mature columnar cells, only 3 incorporated label. Most of the labeled cells were located near the basement membrane. In the L gallbladders, the percentage of labeled cells was approx 23 times higher (0.77%-8.38%, mean 3.30%), and the number of mitoses was significantly increased (mean mitotic index, 1.23%). The labeled cells were randomly distributed in the glands and in the numerous mucosal folds and crests. The uptake of  $^3\text{H}$ -thymidine was not restricted to the "basal" epithelial cells, as it was in the N gallbladder, but occurred mainly in the epithelial columnar cells. To the extent that labeled "basal" cells in the N gallbladder represent the progenitor cells of the gallbladder epithelium, the data indicate that not only quantitative but qualitative changes occur during mucosal cell proliferation in the human L gallbladder. This modified kinetic behavior may be similar to the early proliferative changes described in precancerous lesions of digestive tract mucosa. (25 refs.)

- 78-0533 **Ultrastructure of Cell Junctions in FANL-induced Urothelial Tumors in Urinary Bladder of Fischer Rats.** (Eng) Pauli, B. U. (Dept. Pathology, Rush Medical Coll., Chicago, IL 60612); Weinstein, R. S.; Arai, J.; Arai, M. *Lab Invest* 37(6): 609-621; 1977.



The cell junctions in N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT)-induced tumors of the urinary bladder in male Fischer rats were studied. The rats were fed a diet containing 0.2% FANFT for 26 wk; they were then examined at 26, 43, 51, and 61 wk. All tumors examined prior to 61 wk were noninvasive; 2/3 examined at 61 wk extended into the muscularis mucosa and invaded the blood vessels. In noninvasive tumors, some epithelial zonulae occludentes were focally expanded while others were markedly attenuated. Fasciae or maculae occludentes developed as the tumors became invasive. Gap junctions of both the PF-1 and PF-2 types were present in normal urothelium but no PF-2 junctions were present in the tumor cells. There was little change in desmosomes between normal and tumorous cells, but in tumor cells, the av size and number increased with degree of squamous differentiation. Regional loss of desmosomes and hemidesmosomes were observed in invasive tumors. Since these intercellular junctions are ultrastructurally similar to those in humans, the rat may be a good model for investigation of the early stages of bladder carcinogenesis. (56 refs.)

78-0534 **Bladder Cancer and Squamous Metaplasia in Spinal Cord Injury Patients.** (Eng) Kaufman, J. M. (2045 Franklin St., Denver, CO 80205); Fam, B.; Jacobs, S. C.; Gabilondo, F.; Yalla, S.; Kane, J. P.; Rossier, A. B. *J Urol* 118(6): 967-971; 1977.

The presence of squamous metaplasia and bladder cancer was investigated in 62 patients with spinal cord injuries. There were four groups of patients: Group 1 (25) had a permanent catheter for > 10 yr; Group 2 (24) had a permanent catheter for < 10 yr; Group 3 (11) had short-term catheter drainage; and Group 4 comprised 2 patients whose bladders had been defunctionalized 2-3 yr previously. Squamous cell carcinoma was found in 6/62 patients; 5 also had evidence of transitional cell carcinoma. Five of the cancers occurred in Group 1; the other cancer patient had been without a catheter for 27 yr, after 4 yr of suprapubic drainage. In Group 1, all patients had diffuse chronic cystitis, 20 had extensive squamous metaplasia, 2 had chronic cystitis only, and 3 had cystitis glandularis only. In Group 2, 10 had squamous metaplasia, 2 had cystitis glandularis, and 1 had cystitis cystica. In Group 3, 1 patient was excluded because of recent treatment; the remaining 10 had mild to moderate chronic cystitis, and 2 had squamous metaplasia. In Group 4, one had squamous metaplasia and one had cystitis only. Squamous metaplasia of the proximal and distal urethra was found in 67%, 36%, and 44% of the patients in Groups 1, 2, and 3, respectively. The duration of indwelling catheterization was concluded to be a major factor in the production of squamous changes in these patients. (31 refs.)

78-0535 **Ultrastructural Changes of the Liver in Human and Experimentally Induced Fulminant Hepatitis** (Meeting Abstract). (Eng) Nagata, E. (2nd Dept. Medicine, Kurume Univ. Sch. Medicine, Kurume, Japan); Ikejiri, N.; Eguchi, T.; Kawaguchi, M.; Tanikawa, K. *J Electron Microscop* (Tokyo) 26(3): 229-230; 1977. (no refs.)

78-0536 **Hepatoma in a Child with Methotrexate-induced Hepatic Fibrosis.** (Eng) Ruymann, F. B. (Dept. Pediatrics, Walter Reed Army Medical Center, Box 538, Washington, DC 20012); Mosijczuk, A. D.; Sayers, R. J. *JAMA* 238(24): 2631-2633; 1977.

Autopsy of an 11-yr-old girl with a 6-yr-history of acute lymphocytic leukemia revealed hepatocellular carcinoma with vascular, lymphatic and stromal invasion by malignant hepatocytes. The hepatic fibrosis accompanying the tumor was believed to have been induced by the 2.5 g cumulative dose of methotrexate over 5.5 yr of treatment. This is the first association of hepatoma with methotrexate-induced hepatic fibrosis. (11 refs.)

78-0537 **A Family with Multiple Malignancies, a Malformation Syndrome, and Depressed In Vitro Immune Responsiveness** (Meeting Abstract). (Eng) McKeen, E. A. (NCI, Bethesda, MD 20014); Mulvihill, J. J. *Am J Hum Genet* 29(6): 72A; 1977. (no refs.)

78-0538 **Cancer in Xeroderma Pigmentosum Families** (Meeting Abstract). (Eng) Swift, M. (Univ. North Carolina, Chapel Hill, NC); Chase, C. *Am J Hum Genet* 29(6): 105A; 1977. (no refs.)

78-0539 **Wound Implantation-A Surgical Hazard.** (Eng) Alagaratnam, T. T. (Dept. Surgery, Univ. Hong Kong, Queen Mary Hosp., Hong Kong); Ong, G. B. *Br J Surg* 64(12): 872-875; 1977.

A 60-yr-old man had a squamous cell carcinoma of the posterior third of the tongue that involved the laryngopharynx, alveolus of the right lower jaw, the floor of the mouth, and lymph nodes on both sides of the neck. He underwent total glossectomy with partial excision of the floor of the mouth and right mandible, laryngectomy, and bilateral block dissection of the lymph nodes. Gastrostomy was performed for feeding. Two years later metastatic squamous cell carcinoma was diagnosed at the gastrostomy scar. Subtotal gastrectomy was performed, but the patient died several months later. Autopsy failed to reveal any recurrence in the mouth or pharynx. It is believed that the metastases resulted from wound implantation during the original operation. Data on similar cases from the literature are reviewed. (37 refs.)

78-0540 **Peutz-Jeghers Syndrome. Experience with Twenty Patients in Five Generations.** (Eng) McAllister, A. J. (511 Medical Arts Building, Salt Lake City, UT 84111); Richards, K. F. *Am J Surg* 134: 717-720; 1977.



The pedigree of a family in which 18/21 members over a five-generation span have Peutz-Jeghers syndrome is presented. The case report of one member, a 17-yr-old woman, is presented. The history and anatomic features of the disease are reviewed. (15 refs.)

- 78-0541 Ultrastructural and Metabolic Determinants of Resistance to Azo-Dye and Susceptibility to Nitrosamine Carcinogenesis of the Guinea-Pig.** (Eng) Bryant, G. M. (Dept. Medicine, Tulane Medical Center, New Orleans, LA); Sohal, R. S.; Argus, M. F.; Arcos, J. C. *Br J Cancer* 36(6): 678-691; 1977.

The activities of azo dye reductase (ADR) and nitrosamine dealkylase (ND) in normal, azo dye- and nitrosamine-fed male Sprague Dawley rats and English short-haired albino male guinea pigs were determined. The pigs received 0.12%, the rats 0.06% 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) in the diet for 6 wk. Diethylnitrosamine (DEN) was administered for 10 wk in the drinking water at rates of 1.2 mg/pig/day and 0.65 mg/rat/day. In contrast to the premalignant liver, guinea pig tumor cells had a proliferation of the rough endoplasmic reticulum (RER), little smooth ER, mitochondria with structural variations, an absence of glycogen, and breaks in the nuclear envelope. In the rat, administration of both DEN and 3'-Me-DAB brought about proliferation of smooth ER and sparsity of RER in both premalignant and malignant hepatic tissue. Six weeks of 3'-Me-DAB decreased microsomal protein by 17% in the rat and increased it by 34.6% in the pig; during DEN treatment, there was a 15% increase in the former and a 12.4% decrease in the latter. Administration of 3'-Me-DAB for up to 15 wk did not affect the RNA/protein ratio. 3'-Me-DAB produced a 76% decrease of ADR in the rat but only a 32% decrease in the pig; DEN had no effect on ADR in the latter but increased it by 40.8% in the former. ND activity was unchanged by DEN in both species. 3'-Me-DAB decreased ND activity by 30.4% in the rat and increased it by 53.2% in the pig. Neither compound influenced the starvation-induced increase in ADR in rats; this increase was absent in pigs. The starvation-induced ND increase was suppressed by DEN in the rat and to a lesser extent, in the pig. p-Chloromercuribenzoate (p-CMB) decreased the absorbance of guinea pig liver microsomes; post-p-CMB administration of DEN reduced this decrease. Administration of DEN prior to p-CMB had no effect. Feeding of 3'-Me-DAB had no effect on absorbance. (46 refs.)

- 78-0542 Release of Tumor Cells.** (Eng) Kleinerman, J. (Dept. Pathology, Div. Pathology Res., Saint Luke's Hosp., Cleveland, OH 44104); Liotta, L. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 135-143; 1977.

Tumor cell release was studied in the syngeneic T241 fibrosarcoma-C57BL murine system (which has a femoral growth site) because of its rapid and reproducible metastatic behavior to the lungs. Perfusion of the tumor vascular bed allowed quantitation of tumor cells and clumps in the tumor venous effluent (TVE). Tumor cell concentration in the TVE rose exponentially following postimplant day 4, and tumor cell appearance corresponded directly with the first microscopic evidence of tumor neovascularization. A total of  $10^4$  cells was released on day 5,  $10^5$  cells on day 15. Clumps survived longer than single cells in the vessels; therefore, they initiated more metastases per tumor cell than the same number of single cells. Tumor cell concentration was related to the number of tumor vessels, and clump size distribution was related to vessel size (diameter) distribution. Transplantation of the tumor in admixture with BCG ( $1 \times 10^6$  organisms) reduced the concentration of effluent tumor cells (from a control value of 38 to 16 tumor cells/ml) and clumps (from 43 to 13) and increased the number of effluent tumor cells attached to macrophages (from 0.04 to 0.18). Tumor cells collected in the TVE showed a significantly greater ability to break down basement membrane and purified collagen than did tumor cells from the primary tumor mass. Tumor cells that form metastases may be part of a subpopulation that has special biological and immunogenic properties. However, tumor cells entering the circulation may also be conditioned by their environment. (22 refs.)

- 78-0543 Electron Microscopic Study of a Sacral Chordoma. Characterization of Various Stages of Tumor Cell Evolution.** (Fre) Thiery, J. P. (Fondation-Curie, Institut du Radium, 26, rue d'Ulm, 75231 Paris Cedex 05, France); Mazabraud, A.; Mignot, J.; Durigon, M. *Ann Anat Pathol (Paris)* 22(2): 193-204; 1977.

Electron microscopy observations on the evolution of tumor cells in a sacral chordoma from a 32-yr-old man are presented. Although young cells contained little glycogen, glycogen accumulated with age to a point where it almost filled the entire cytoplasm. As evolution progressed, however, the amount of glycogen decreased and was eventually incorporated into vacuoles. All the chordoma cells were active, and none could be considered senescent. Enzymatic lysis of polysaccharides could be the cause of the vacuolation that produces the physaliphorous cell. A comparison of the chordoma cells and those of a normal notochord indicates some morphological similarities in their development. The evolutionary data can be used to classify various types of chordomas. (13 refs.)

- 78-0544 Organ Distribution of Intravenously Injected Tumor Cells as a Function of Cell Surface Charge.** (Eng) Lalwani, N. D. (Biophysics Div., Cancer Res. Inst., Bombay 400 012, India); Shenoy, C. N.; Chaubal, K. A. *Indian J Exp Biol* 15(8): 606-608; 1977.



Untreated and heparin- or dextran sulfate-treated fibrosarcoma and ascites tumor cells were labeled with  $^{51}\text{Cr}$  and injected iv into syngeneic Swiss mice. The higher negative charge of the treated cells resulted in their increased deposition in lungs, liver, kidney, and spleen. (19 refs.)

8-0545 **Fibrin-bound Tumour Cells on a Sclerosed Mitral Valve.** (Eng) Donald, K. J. (Dept. Pathology, Univ. Queensland, Medical Sch., Herston Road, Herston, Queensland 4006, Australia); Chalk, S.; Sullivan, J. J. *Pathology* 9(3): 195-198; 1977.

Tumor cells were found on the mitral valve of a 62-yr-old woman with a long history of rheumatic heart disease. Two months later, she was found to have bilateral poorly differentiated ovarian carcinoma. The carcinoma cells were associated with fibrin and were PAS negative, as was the ovarian tumor tissue. Although the possibility of a primary mitral sarcoma has not been ruled out, it is suggested that the sclerosed mitral valve provoked local fibrin deposition that trapped circulating malignant cells. These findings support the hypothesis that local fibrin deposits may encourage formation of metastases in man. (6 refs.)

8-0546 **Significance of Fibrin/Fibrinogen for the Growth and Metastasis of Malignant Tumors.** (Ger) Heyes, H. (Univ. Frauenklinik, Prittwitzstrasse 43, D-7000 Ulm/Donau, W. Germany); Gluck, D. *Klin Wochenschr* 55(22): 1079-1087; 1977.

Studies of the role of fibrinogen and fibrin in the growth and metastasis of malignant tumors are reviewed. Tumor cells adhering to the vessel wall become enveloped in a network of fibrin, and they penetrate the wall by ameboid movement. Tumor cell survival is then temporarily facilitated by the fibrin, which serves as a source of proteins and amino acids and protects the tumor cells from the defense mechanisms of the body. A fibrin clot is necessary for vascularization, which is a prerequisite of the survival and growth of metastases. Malignant tumors are able to convert fibrinogen into fibrin as a result of the properties of their vessels and cells. An accumulation of fibrin and fibrinogen was observed in many experimental tumors. (118 refs.)

8-0547 **Role of Surface Glycoproteins in Tumor Growth.** (Eng) Cooper, A. (Dept. Pathology, Tufts Univ. Medical Sch., Boston, MA 02111); Morgello, S.; Miller, D.; Brown, M. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Mansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 49-64; 1977.

Many requirements for metastasis involve the tumor cell surface, on which glycoproteins (gp) probably play an important role in cell-cell interaction. Therefore, the implantation and

growth of two sublines of the murine  $\text{TA}_3$  adenocarcinoma,  $\text{TA}_3\text{-Ha}$ , which contains a large amount of high-mol wt gp (GP-I) on its surface, and  $\text{TA}_3\text{-St}$ , which lacks GP-I, were studied. The *Vicia graminea* lectin assay was used to measure GP-I on the cells. GP-I levels on Ha cells grown for the first time at an sc site were much lower than those on cells grown at an ip site, which probably accounts for the poor take rate of ascites-grown Ha tumors placed sc in allogeneic mice. The low GP-I levels were reversible when the sc-grown cells were put back ip or when Ha was passaged sequentially in several recipients in the sc site. This reversibility could have an important effect on the ability of a  $\text{TA}_3$  line to implant or metastasize, since a solid metastasis may be more allied to a solid sc growth than to the ascites form. Attempts were made to select for tumor cells capable of wide dissemination in syngeneic mice following tail vein injection. Cells of an Ha variant that metastasized spontaneously from an ip injection site to the sc tissue of the back and thigh were used. Selection for high-rate spread to the liver was successful. The selected cells consistently had large numbers of *V. graminea* lectin receptors, presumably because of large numbers of GP-I surface molecules. In vitro, the selected line also synthesized and released into the medium three times as much GP-I as the standard Ha subline. Finally, the selected line released three times as much *V. graminea* lectin-inhibiting gp, which correlated with the increase noted on the intact cell surface. These gp changes associated with the selected line may be involved in enhanced tumor spread. (20 refs.)

See also:

\*(Rev.): 78-0015, 78-0017, 78-0028, 78-0032, 78-0046, 78-0061, 78-0066, 78-0089, 78-0090, 78-0091, 78-0092, 78-0093, 78-0094, 78-0095, 78-0096, 78-0097, 78-0098, 78-0101, 78-0103, 78-0104, 78-0106, 78-0107, 78-0109, 78-0110.

\*(Chem.): 78-0121, 78-0123, 78-0126, 78-0127, 78-0129, 78-0131, 78-0134, 78-0139, 78-0142, 78-0147, 78-0150, 78-0151, 78-0153, 78-0154, 78-0155, 78-0161, 78-0167, 78-0168, 78-0169, 78-0179, 78-0182, 78-0185, 78-0186, 78-0189, 78-0193, 78-0200, 78-0211, 78-0214, 78-0216, 78-0221, 78-0222, 78-0226, 78-0227, 78-0229, 78-0230, 78-0232, 78-0237, 78-0240, 78-0241, 78-0245, 78-0256, 78-0259, 78-0265, 78-0268, 78-0269, 78-0272, 78-0273.

\*(Phys.): 78-0277, 78-0279, 78-0280, 78-0281, 78-0283, 78-0286, 78-0296, 78-0297, 78-0298.

\*(Viral): 78-0311, 78-0312, 78-0342, 78-0355, 78-0374, 78-0376, 78-0380, 78-0396, 78-0405, 78-0409, 78-0411, 78-0412, 78-0417.

\*(Immun.): 78-0431, 78-0432, 78-0434.

\*(Epid.-Biom.): 78-0552, 78-0560, 78-0568, 78-0572, 78-0577.



## EPIDEMIOLOGY AND BIOMETRY

- 78-0548 Influence of Height, Weight and Obesity on Risk of Breast Cancer in an Unselected Swedish Population.** (Eng) Adami, H. O. (Dept. Surgery, Univ. Hosp., S-700 14 Uppsala, Sweden); Rimsten, A.; Stenkvist, B.; Vegelius, J. *Br J Cancer* 36(6): 787-792; 1977.

The influence of height, wt, and obesity on risk of breast cancer was examined in 179 breast cancer patients and an equal number of age-matched controls. There were 70 women with Stage I disease, 85 with Stage II, 16 with Stage III, and 8 with Stage IV; the median age was 64 yr. There were no differences in the distribution of height and wt between the patient and control groups. This lack of correlation persisted when women with Stage IV disease were excluded because of their reduced wt. (26 refs.)

- 78-0549 The Epidemiology of Mammary Carcinoma (Meeting Abstract).** (Ger) Mastny, K. H. (Erfurt, E. Germany); Pothe, H. *Zentralbl Chir* 102(23): 1461-1462; 1977. (no refs.)

- 78-0550 A Statement by the Labor Safety and Health Institute.** (Eng) Anonymous (No affiliation given). In: *Proceedings Conference on Women and the Workplace, June 17-19, 1976, Washington, D.C.* Society for Occupational and Environmental Health. (Washington, DC): 364 pp.; 361-364; 1976.

The effect of lead on the female reproductive system and the transplacental effects of benzo(a)pyrene make women particularly susceptible to certain occupational hazards. Steps should be taken to identify and eliminate other potential hazards to men and women alike. (no refs.)

- 78-0551 Is There a Changing Epidemiology of Premalignant Lesions of the Cervix? Results of Cytologic Screening of Pregnant Women.** (Eng) Fredricsson, B. (Dept. Obstetrics and Gynecology, Sabbatsberg Hosp., 113 83 Stockholm, Sweden); Nasiell, M.; Sennerstam, R.; Wadas, A. M. *Acta Obstet Gynecol Scand* 56(4): 435-439; 1977.

The incidence of premalignant changes in the uterine cervix of 2,394 women screened between 1961 and 1964 was compared to the incidence in 2,384 women screened in 1972. An

abnormal cytology was noted in 135 women in the first sample and 170 women in the second, a statistically significant difference. A comparison of the age distribution of all changes showed higher incidence in the 21-25 and 26-30 age groups in 1972 compared to 1964. The proportion of Pap III and IV atypias increased in 1972, especially among teenagers and women aged 31-40 yr. There were not enough carcinomas in situ to draw any conclusions about a changing incidence. The increased frequency of atypias in women between 21 and 30 focuses attention on the possibility that the epidemiology of cervical cancer is changing. (11 refs.)

- 78-0552 Haemoglobin Genotype, ABO Blood Groups and Carcinoma of the Cervix.** (Eng) Adelusi, B. (Dept. Obstetrics and Gynaecology, Univ. Ibadan, Ibadan, Nigeria). *J Trop Med Hyg* 80(7): 152-154; 1977.

A study was made to determine the relationship, if any, between Hb genotype or ABO blood groups and carcinoma of the cervix. The test population comprised 114 patients with cervical carcinoma; 36 patients with a histologic diagnosis of cervical erosion, chronic cervicitis, and vaginal warts; and 3,000 (Hb study) and 26,027 (blood-group study) controls. Most of the cancer patients had Hb genotypes A and AS, but there was no significant difference between the observed (69.3% for A and 24.6% for AS) and expected (66.0% and 25.6%, respectively) distributions. Most of the cancer patients belonged to blood group O, but again there was no significant difference between the observed and expected distributions (54.4% vs 51.5%). The values for the other patient groups were similar. (18 refs.)

- 78-0553 Cervical Cancer. Mass Screening, Incidence and Mortality in Finland.** (Eng) Timonen, S. (First Dept. Obstetrics and Gynaecology, Helsinki Univ. Central Hosp., Helsinki, Finland); Pyorala, T. *Acta Obstet Gynecol Scand [Suppl]* (67): 13-19; 1977.

Since a Finnish screening program for cervical cancer was initiated in the early 1960's, the rate of participation has been between 75% and 97%, and the number of new cases of cervical cancer has dropped. The lowest number to date occurred in 1975, when only 230 new cases were diagnosed. Previously, the annual record of new cases was between 350 and 450. The decrease was most evident in the younger age group. The rate of diagnosis of carcinoma in situ has also



increased, but it has not surpassed that of new cancers. However, the incidence of the precancerous stages is about 150% of the incidence of cancer. In 1975, the incidence of invasive cancer and carcinoma in situ was  $7.0 \times 10^{-5}$  and  $6.2 \times 10^{-5}$ , respectively. Mortality has been eliminated completely in the 35-year age group, but only a slight decrease has been noted in patients of a more advanced age. It is estimated that the current incidence and mortality values are about half of those that existed at the beginning of the project. (9 refs.)

78-0554 **Mass Screening in Sweden for Cancer of the Uterine Cervix. Results and Epidemiologic Effect.** (Eng) Kjellgren, O. (Dept. Gynaecological Oncology, Univ. Umea, S-901 85 Umea, Sweden). *Acta Obstet Gynecol Scand [Suppl]* (67): 5-11; 1977.

The screening program for cancer of the uterine cervix in Sweden is reviewed. Since the program was initiated in 1964, between 55% and 90% of the women are screened every year. During the years 1967-1974, the positive cytology rate varied between 1.8% and 1.1%. Positive smears in Papanicolaou group IV decreased from 0.4% to 0.2%, those in Group V from 0.4% to 0.1%. During this time, the incidence also dropped, as shown by the figures of 221/million between 1958 and 1971 and 189/million during 1971. This decrease is particularly evident in the younger cohorts. The peak incidence appears to be in the 48- to 45-yr age group, with a tendency to decreasing incidence in the later years. Mortality has remained constant at about 80/million. The diagnosis of in situ cervical cancer has increased remarkably from 200/million in 1964 to approx 1,000/million in 1971; the peak incidence for cancer in situ appears to be at approx 30 yr of age. (8 refs.)

78-0555 **Gynecological Cancer in the Maltese Islands.** (Eng) Sultana, H. M. (Radiotherapy Dept., St. Luke's Hosp., Guardamangia, Malta); Camilleri, A. P. *Gynecol Oncol* 5(4): 346-356; 1977.

An analysis was made of the incidence of various forms of gynecological cancer (318 cases) in the Maltese Islands during 1969-1973. When analyzed by site, endometrial carcinoma was the most common form, being 1.8 and 2.4 times more common than ovarian and cervical cancer, respectively. The histological picture conformed to the usual frequency and variation patterns. There was a significantly low incidence of cervical cancer and a high incidence of corpus cancer. The low incidence of cervical cancer may be due to the absence of early sexual activity and lack of multiple partners, characteristics that were almost universal in Maltese women until 10-20 yr ago. A rising incidence of cervical cancer may occur in the near future if sexual activity does have an important causative role. (15 refs.)

78-0556 **The Frequency of Bronchogenic Carcinoma with Respect to Some Risk Factors in Selected Districts of Prague.** (Cze) Trefny, J. (Vyzkumny ustav tuberkulozy a respiracnich nemoci, 180 71 Prague 8- Bulovka, Czechoslovakia). *Cas Lek Cesk* 116(36): 1114-1118; 1977.

A total of 628 adults from three districts of Prague, with an av of 177,000 residents, developed malignant respiratory tract neoplasms over a 15-yr period. The mean annual incidence of these tumors, 80% of which were bronchogenic carcinomas, was 53/100,000. Morbidity from the bronchogenic carcinomas did not vary significantly from one district to another or during the years under study. However, the morbidity rate was 6.8 times higher in women with tubercular or fibrotic lung lesions than in women without these lesions. Men with the lesions had a bronchogenic carcinoma morbidity rate 2.3 times higher than men without them. When the rates were adjusted to account for smoking habits, morbidity 2.2 times as high in men aged 40-64 yr with the fibrotic lesions as in men of a similar age range without the lesions. The mean annual mortality from the bronchogenic carcinomas was 88/100,000. (14 refs.)

78-0557 **Lung Cancer Mortality in a Steel Foundry.** (Eng) Gibson, E. S. (Dept. Clinical Epidemiology and Biostatistics, McMaster Univ., P.O. Box 460, Hamilton, Ontario L8N 3J5, Canada); Martin, R. H.; Lockington, J. N. *J Occup Med* 9 19(12): 807-812; 1977.

Lung cancer mortality was examined in 1,542 foundry and nonfoundry steel workers who were alive and at least 45 yr of age in 1967. They were followed until 1977. Death due to lung cancer occurred in 21/439 foundry workers and 11/1,103 nonfoundry workers; the difference was significant between the ages of 45 and 64. On the av, a foundry worker was five times more likely to die of lung cancer than a nonfoundry worker after age 45. Comparison with metropolitan Toronto mortality rates indicated a significant excess of lung cancer in the foundry group. Foundry workers showed an overall standardized mortality ratio (SMR) for lung cancer of 250, nonfoundry workers, an SMR of 6. The highest SMR's were noted in crane operators (714), followed by finishers (314), molders (255), coremakers (208), and electric furnace/open hearth operators (114). There was a significant difference between observed and expected deaths after 5 yr of exposure. (13 refs.)

78-0558 **Risk Factors for Lung Cancer in Singapore Chinese, a Population with High Female Incidence Rates.** (Eng) MacLennan, R. (International Agency Res. Cancer, Lyons, France); Da Costa, J.; Ng, Y. K.; Day, N. E.; Law, C. H.; Shanmugaratnam, K. *Int J Cancer* 20(6): 854-860; 1977.



To evaluate the increased risk of lung cancer from cigarette smoking and other possible risk factors, Chinese men and women and hospital controls were studied in Singapore during 1972-1973. The female cases were divided into Cantonese and non-Cantonese groups because of the high incidence of lung cancer among the former. A significant dose-response effect of cigarette smoking was found for all male and female groups, but neither smoking nor any other factor was found that could account for the high incidence of lung cancer in Cantonese women. They exhibited high rates of adenocarcinoma. The finding over all sex and dialect groups of a significantly increased risk of lung cancer in persons with a low consumption of selected vegetables (mainly dark-green leafy types) was unexpected but consistent with a previous report of a possible association between lung cancer and low vitamin A intake. (15 refs.)

- 78-0559 **Lung Cancer in Coastal Georgia: A Death Certificate Analysis of Occupation: Brief Communication.** (Eng) Harrington, J. M. (TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England); Blot, W. J.; Hoover, R. N.; Housworth, W. J.; Heath, C. W.; Fraumeni, J. R. *J Natl Cancer Inst* 60(2): 295-298; 1978.

Lung cancer mortality rates are exceptionally high among white male residents in several counties along the Southeastern Atlantic coast of the US. In a preliminary study, occupations listed on the death certificates of 858 white men who lived in Georgia coastal counties and who died of lung cancer during 1961-1974 were analyzed and compared with those of 858 age- and residence-matched controls. There was a two-fold increased risk associated with the construction industry [estimated risk (er) 2.04] and nearly a 50% increase with chemical-related industry (er 1.46). About 25% more cancer patients than controls were employed in the two largest industrial categories, the wood and paper (er 1.28%) and transportation operation (er 1.25). There was a threefold excess risk (relative risk 3.3) of lung cancer in wood and paper industry workers from the smaller rural coastal counties, but not in these workers in the three largest urban coastal counties (relative risks 1.0, 0.8, 0.3). The urban-rural difference may indicate variations in type and length of industrial exposures. (7 refs.)

- 78-0560 **Atrophic Gastritis: Its Genetic and Dynamic Behavior and Its Relations to Gastric Carcinoma and Pernicious Anemia.** (Eng) Siurala, M. (Dept. Medicine, Univ. Helsinki, Helsinki, Finland); Villako, K.; Ihmaki, T.; Kekki, M.; Lehtola, J.; Sipponen, P.; Varis, K. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 135-150; 1977.

Six families and two random series of patients with atrophic gastritis were studied, and the results were subjected to computer analysis. Gastritis appears to be a progressive disease, but spontaneous improvement and return to normal are possible. Superficial gastritis is usually an obligatory precursor of atrophic gastritis; in adults, fundic gastritis is a progressive and mostly irreversible process. A comparison of antral and fundic gastritis indicates that the former begins at an earlier age, but progression of the latter is more rapid. Follow-up studies of 377 outpatients indicated that atrophic gastritis always preceded the occurrence of benign and malignant tumors. However, this change is not obligatory: one random study found a 26% incidence of gastritis but only 2 gastric carcinomas among 1,400 inhabitants of a rural district. The outpatients with gastric carcinoma (11/377) had a significantly higher incidence of pernicious anemia than the general population (7.5% vs 0.15%). Analysis of the family studies suggests that a genetic factor is involved in atrophic gastritis, particularly the A type, and that the mode of inheritance is probably multigenetic. Atrophic gastritis and gastric carcinoma accumulated in families of probands with pernicious anemia. Furthermore, the transition risk from one degree of gastritis to a more severe one was markedly increased in relatives of patients with severe atrophic gastritis and pernicious anemia compared with controls. These results suggest a genetically influenced relationship between atrophic gastritis, pernicious anemia, and gastric carcinoma. (26 refs.)

- 78-0561 **Gastric Cancer in the Hawaii Japanese.** (Eng) Stemmermann, G. N. (Kuakini Medical Center, 347 N. Kuakini St., Honolulu, Hawaii 96817). *Gann* 68(5): 525-535; 1977.

The gastric cancer experience of the Hawaii Japanese is reviewed, along with the current status of the geography, demography, epidemiology, pathology, and behavior of this disease in the Hawaiian Islands. It is proposed that invasive tumors result from a change of the normal gastric mucosa into mucosa that resembles that of the small intestine, a mutation caused by exposure of the mucosa to nitroso compound formed by the nitrosation of dietary amines. The frequency of gastric cancer is decreasing among second-generation Hawaii Japanese, but high rates persist in the first generation. This difference is due to the decreased consumption of food rich in salt and nitrate and a concomitant increased consumption of fresh fruit and vegetables in the former. The nitrosation of dietary amines may be blocked by ascorbic acid. Intestinalized gastric mucosa is at increased risk of ulcer and cancer, which explains the similar epidemiology of the two conditions. The differences in survival for the diffuse and intestinal types of tumors, the influence of sex on survival with diffuse cancer, racial differences in the frequency of diffuse cancer, and the different patterns of metastatic spread from these two types of cancer imply a strong host influence on the morphology and behavior of gastric cancer. (32 refs.)



78-0562 **Frequency and Relevance of Focal Carcinomas in Adenomatous Polyps of the Colon (Meeting Abstract).** (Eng) Frimberger, E. (I. Medizinische Abteilung Stadt. Krankenhaus, Oskar-Maria-Graf-Ring 51, 8000 Munich 83, W. Germany); Kuhner, W.; Kunert, H.; Seib, H. J. *Endoscopy* 9(3): 193-194; 1977. (no refs.)

78-0563 **Comparison of the Fecal Microflora of Seventh-Day Adventists with Individuals Consuming a General Diet. Implications Concerning Colonic Carcinoma.** (Eng) Goldberg, M. J. (Dept. Internal Medicine, Univ. Illinois Hosps., Chicago, IL); Smith, J. W.; Nichols, R. L. *Ann Surg* 186(1): 97-100; 1977.

The fecal microflora of 14 Seventh-Day Adventists who had not eaten meat for at least 10 yr and 14 individuals on a general American diet were compared. No statistically significant differences were noted. Dietary fat apparently does not alter fecal microflora significantly; however, this does not invalidate the concept that dietary animal fat increases bile acid degradation, a factor that has been related to colonic cancer. (26 refs.)

78-0564 **Diet Fiber and Colonic Cancer (2 Letters to Editor).** (Eng) Lyon, J. L. (Univ. Utah Medical Center, Salt Lake City, UT); Mendeloff, A. I. *N Engl J Med* 298(2): 110-111; 1978.

The question of whether beef protein and saturated fats are more important than dietary fiber in the epidemiology of colonic cancer is debated. (9 refs.)

78-0565 **Epidemiology of Premalignant Gastric Lesions.** (Eng) Correa, P. (Louisiana State Univ. Medical Center, New Orleans, LA); Cuello, C.; Haenszel, W. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976.* The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 13-179; 1977.

The epidemiology of premalignant gastric lesions in Narino, region in southern Colombia in which there is a high incidence of gastric cancer, was investigated. Adult biopsies showed a 48% incidence of chronic atrophic gastritis without demonstrable intestinal metaplasia. Plots of inhabitants with and without gastritis showed definite boundaries between the two populations. Although there were no differences in nitrate content in water from aqueducts in high- and low-risk areas, there was a significantly higher nitrate content in water from dug wells in the high-risk area. Fur-

thermore, urinary nitrate concentration was significantly higher in the high-risk area. A study of food consumption indicated that corn and moras (a native berry of high acid content) were positively associated with intestinal metaplasia and gastritis but that lettuce had a protective effect. High nitrite levels were found in the gastric juice of 25/79 Narino inhabitants. This level was positively correlated with an abnormally elevated gastric pH, a condition known to lead to bacterial colonization of the gastric mucosa. (14 refs.)

78-0566 **The Oesophageal Carcinoma Problem in Transkei: A Geographic Reappraisal.** (Eng) McGlashan, N. D. (Dept. Geography, Univ. Tasmania, Hobart 7001, Australia). *S Afr J Sci* 73(10): 294-299; 1977.

A geographic plot of the home districts of 79 Transkei miners, who were returned to their homes because of esophageal cancer and of the home districts of 1,554 Transkei residents with the same cancer reveals a remarkable overlap in the regions of highest incidence. Cancer incidence increases as one goes from northeast to southwest. The etiological agent responsible for this cancer is apparently social rather than physical, because the physical environment variation is on an axis at right angles to that of the disease (the 2 axes oppose each other). The pattern of primary liver cancer is similar to that of esophageal cancer. It is postulated that varying degrees of exposure to the same carcinogen could account for both these cancers. Because of the noticeable demarcation between areas of high and low incidence, study of only a few high- and low-risk areas should provide sufficient etiologic data. Nitrosamines, mycotoxins (aflatoxins), and tobacco merit investigation as possible etiologic agents. (21 refs.)

78-0567 **Cancer of the Esophagus in Djibouti. Report of 36 Cases Collected in Two Years.** (Fre) Gen-dron, Y. (Hopitaux des Armees, Djibouti, French Somaliland, E. Africa); Ardouin, C.; Lassalle, Y.; Sirol, J. *Bull Soc Pathol Exot* 70(1): 74-82; 1977.

In an African hospital, 36 patients (29 men, 7 women aged 40-70 yr) with cancer of the esophagus were observed within a 2-yr period. Clinical symptoms included dysphagia, regurgitation, and pain, and diagnosis was established by radiography in all patients and biopsy specimens obtained by fibroscopy in 24. Only palliative therapy was attempted, since the cancers were well-advanced, and they coexisted with hepatomegaly and/or subclavicular adenopathy in 14 patients. The patients were all African orientals who chewed the leaf of the Khat shrub, which was suspected as being the etiological factor because the active principle of the plant is an alkaloid. Esophageal endoscopic examination of 50 patients (aged 20-40 yr) with duodenal ulcers who chewed 100-300 g of Khat daily revealed a nonspecific inflammation in only 2. Exami-



nation of 30 men (aged 30-60 yr) who consumed larger quantities, 200-500 g/day over a 15-yr period and who smoked 20-40 cigarettes/day revealed only 1 case of esophagitis. Khat cannot be ruled out as an etiological factor, since the number in this series was small. Genetic factors may be predisposing to esophageal cancer, as it is prevalent only among the various ethnic populations who habitually chew Khat. (12 refs.)

- 78-0568 Skin Cancer of the Hand and Arm in Sweden 1966-70 in Relation to Previous Occupational Exposure.** (Eng) Wahlberg, J. E. (Dept. Occupational Dermatology, Karolinska Sjukhuset, S-104 01 Stockholm, Sweden); Johansson, G. *Berufsdermatosen* 25(5): 185-195; 1977.

From 1966 to 1970, 399 cases of skin tumor (excluding melanoma) of the hand and arm were reported to the Swedish Cancer Registry. They occurred in 257 men and 142 women. Data from case records were examined to discover if there were contributory factors in the working environment. Most (62.9%) of the patients were > 70 yr old at diagnosis. Nearly 62% of the cases were squamous cell carcinoma (85% on the hand, 15% on the arm), and 23% were carcinoma in situ (65% on the hand, 35% on the arm). The 126 patients who were < 70 yr old at diagnosis were sent a questionnaire, and 91 (53 men, 38 women) responded. In this group, 52% had squamous cell carcinoma 26% carcinoma in situ, indicating that the former occurs more often at higher ages. Seven had had contact dermatitis, 7 radiation exposure, 6 psoriasis, 4 unclassifiable eczema, 4 burn, 3 fracture, and 2 wound; 58 had had no disease or injury. Forty-seven patients had worked indoors, 39 had worked outdoors for 1-50 yr, and 5 had had no occupation. The seven cases of contact dermatitis are of special interest from the point of view of occupational dermatology. (27 refs.)

- 78-0569 Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes.** (Eng) Mancuso, T. F. (Univ. Pittsburgh, Pittsburgh, PA 15261); Stewart, A.; Kneale, G. *Health Phys* 33(5): 369-385; 1977.

Causes of death among workers at the Hanford atomic plant in Richland, WA, were analyzed in relation to radiation exposure. Of 3,250 deaths in the period 1944-1972, 670 were due to cancer and 2,850 to nonmalignant diseases. For 14 bone marrow cancers, the estimated number of radiation-induced cases was 9.3, for 161 cancers of the pancreas or lungs, the estimate was 18.6. The estimate for all cancers (25.8) was a fraction smaller than the sum of the estimates for the three cancers with definite radiation associations (27.9), and the estimate for reticuloendothelial system neoplasms was a fraction larger than that for bone marrow cancers. Thus, the proportion of radiation-induced cancers among exposed workers was probably 6%-7%. Differences between cancer and noncancer deaths were pronounced only

in the period 1958-1972, when the av annual radiation dose of exposed workers was 51.3 centirads for the cancer group and 47.7 for the noncancer group. Workers aged 25-45 yr were less sensitive to the cancer-inducing effects of radiation than older and younger workers. (6 refs.)

- 78-0570 Bone Cancer among Female Radium Workers. Latency Periods and Incidence Rates by Time after Exposure.** (Eng) Polednak, A. P. (Center Human Radiobiology, Radiological and Environmental Res. Div., Argonne Natl. Lab., Argonne, IL 60439). *J Natl Cancer Inst* 60(1): 77-82; 1978.

Bone cancer occurred in 58/1,250 women exposed to radium while they were working in the luminous watch-dial industry between 1913 and 1929. The present analyses (tumor latency periods and incidence rates over time after first exposure) are confined to the 751 women with a measured body radium burden, among whom 36 (of the total 58) bone cancers occurred. The lowest radium intake dose associated with bone cancer was 202.5  $\mu$ Ci. The mean and median bone cancer latency period tended to decline, but av survival among women without bone cancer also decreased with increasing radium intake. In a group of 51 women exposed to 200 to 749  $\mu$ Ci, 1 cancer each was noted between 10 and 14 yr, 15 and 19 yr, 20 and 24 yr, 25 and 29 yr; 3 were noted between 30 and 34 yr, 2 between 35 and 39 yr, 5 between 40 and 44 yr, and 2 > 45 yr. In a group of 40 exposed to 750  $\mu$ Ci, 3 cancers were noted at 5-9 yr, 5 at 10-14 yr, 2 at 15-19 yr, 4 at 20-24 yr, 2 at 30-34 yr, and 1 each at 25-29 yr, 35-39 yr, 40-44 yr, and > 45 yr. Incidence rates were consistently higher in the second group than in the lower dose group at each 5-yr period after exposure. There was no significant variability in the relative odds for bone cancer over time after exposure between one group of women first exposed at < 18 yr of age and another group exposed at > 18 yr. (24 refs.)

- 78-0571 Ultrastructural Autoradiographic Study of Blast Cells in the Mouse Thymus. Interest for Radioleukemia Research.** (Eng) Boniver, J. (Lab. Morbid Anatomy, Inst. Pathology, State Univ. Liege, Sart-Tilman B-4000 Liege, Belgium); Simar, L. J.; Courtoy, R.; Betz, E. H. *Experientia* 33(11): 1505-1506; 1977.

Ultrastructural and autoradiographic studies of C57BL mouse thymus blast cells after inoculation of the mice with <sup>3</sup>H-thymidine 9  $\mu$ Ci/g showed that their fine nuclear structure was related to their position in the cell cycle. The percentage of labeled blasts was influenced markedly by the lymphoblast labeling index. Labeling values were consistent with the presence of X cells in the S phase of the cycle and with the presence of ring-shaped nucleolus cells from the end of S to the beginning of G<sub>1</sub>. The results were compatible with the variations in subcapsular blast cell populations observed



ing radiation-induced leukemogenesis. They indicate that kinetic changes in thymic lymphopoiesis are probably due to the oncogenic process. (6 refs.)

0572 **Characteristics in Youth Predictive of Adult-onset Malignant Lymphomas, Melanomas, and Leukemias.** (Eng) Paffenbarger, R. S. (California State Dept. of Health, 2151 Berkeley Way, Berkeley, CA 94704); Wing, A. Hyde, R. T. *J Natl Cancer Inst* 60(1): 89-92; 1978.

Characteristics predictive of later development of malignant lymphomas, melanomas and leukemias were determined in 1000 male alumni of Harvard Univ. and Univ. Pennsylvania. A history of the common contagious diseases of childhood was predictive of a lower risk of Hodgkin's disease and lymphatic leukemia; varicella increased the risk of malignant lymphomas and leukemia; tonsillectomy was associated with higher risk of leukemia; obesity was predictive of Hodgkin's disease; leanness was associated with other lymphomas; outdoor environmental exposure increased the risk of malignant melanoma. (14 refs.)

0573 **Age-related Differences in the Trends of Fatal Hodgkin's Disease as a Consequence of Immune Deficiency.** (Eng) Szkely, D. R. (Dept. Epidemiology, SC Sch. Public Health and Community Medicine, Univ. of Washington, Seattle, WA 98195); Lee, J. A. *Cancer Res* 37(2): 4568-4571; 1977.

In England and Wales, the mortality rate from Hodgkin's disease doubled from 1911 to 1970. Examination of trends in the age-specific rates with time confirmed the previously reported decline in children and rise in elderly people and revealed a rapid rise in the mortality of young adults of both sexes. These changes were not compatible with any reasonable variations in the diagnosis or classification of Hodgkin's disease. The data are compatible with the hypotheses that the biology of the disease in young adults is different from that in elderly people and that the rise in the mortality of young adults is due to a transfer of deaths from the disease in childhood. It is possible that a number of children (about two thirds to every female) are born with an immune defect that increases their risk of succumbing to childhood infections. If this risk is reduced by antibiotics, the children survive to develop Hodgkin's disease, thus increasing its incidence in young adults. (27 refs.)

0574 **Nasopharyngeal Cancer in a Total Population: Selected Clinical and Epidemiological Aspects.** (Eng) Turgman, J. (Dept. Clinical Epidemiology, Chaim Weizman Medical Center, Tel Hashomer, Israel); Modan, B.; Shoham, M.; Rappaport, Y.; Shanon, E. *Br J Cancer* 36(6): 786-787; 1977.

Nasopharyngeal cancer is discussed based on 150 cases diagnosed in Israel between 1960 and 1968. The patients ranged from 1 mo to 85 yr in age. The annual incidence was 1.0/100,000 for men and 0.4/100,000 for women, and the incidence increased with age in both sexes. There was a significantly higher incidence in North African-born subjects than in European-born persons of both sexes and Asian-born men. The disease occurred at a similar rate in Arabs and Jews. Lymphoepithelioma comprised 42% of the cases, anaplastic carcinomas 26.7%, and squamous cell carcinomas 23.3%. The most common symptom was cervical lymphadenopathy. Patients with lymphoepithelioma had a better prognosis than those with other tumors. Prognosis was also better in patients without invasion of the skull or neurological complications. (15 refs.)

78-0575 **Study of Cancers of the Nasal Fossa and Sinus Cavity in the Lorraine Region.** (Fre) Velten, J. (Strasbourg, France). *Arch Mal Prof* 38(7/8): 701-706; 1977.

A study of 25 patients (20 men, 5 women) with cancer of the nasal fossa reported in the Lorraine region during 1969-1974 revealed that 9 male patients were woodworkers. The tumors in the woodworkers comprised 6 adenocarcinomas, 1 anaplastic carcinoma, and 2 malpighian tumors. The average duration of employment for the woodworkers was 17 yr. In a discussion of the pathogenesis of the neoplasms, it was concluded that tannin is the most likely carcinogen to which the workers were exposed. (no refs.)

78-0576 **The Incidence of Malignancy in Carotid Body Tumor.** (Eng) Gaylis, H. (Dept. Surgery, Univ. of Witwatersrand, Johannesburg, South Africa); Mieny, C. J. *Br J Surg* 64(12): 885-889; 1977.

The cases of 23 patients (20 women, 3 men aged 23-73 yr) with 24 carotid body tumors are reviewed. The tumor was on the right side in 12 patients, on the left in 10, and bilateral in 1. Duration of symptoms varied from 2 wk to 20 yr. Twenty patients were treated surgically, 2 received no treatment, and the remainder received radiation. The incidence of malignancy in this series was 30%; in some cases, it was not possible to determine malignancy until several years later, when metastases to the regional lymph nodes were detected. Complications were limited to larger tumors. Since there is a high rate of malignancy and complications are minimized when the tumors are small, it is suggested that all carotid body tumors be removed unless there are medical or technical contraindications. (18 refs.)

78-0577 **Incidence of Neurofibroma in Cattle in Abattoirs in New South Wales.** (Eng) Doughty, F. R. (Dept. Agriculture, Regional Veterinary Lab., Wagga, Wagga, New South Wales 2650, Australia). *Aust Vet J* 53(6): 280-281; 1977.



The incidence of neurofibroma in slaughtered cattle in New South Wales during 1969-1971 is reported. The tumors were most frequent in adult Hereford females >5 yr old. More than 500 neurofibromas were traced back to the herds of origin, and in 24 of these, the disease had occurred previously. However, there was no significant familial association between the neurofibroma cases. (1 ref.)

- 78-0578 Incidence of Nelson's Syndrome after Adrenalectomy for Cushing's Disease in Children: Results of a Nationwide Survey. (Eng) Hopwood, N. J. (Dept. Pediatrics, Univ. Michigan Medical Center, Ann Arbor, MI 48109); Kenny, F. M. *Am J Dis Child* 131(12): 1353-1356; 1977.

Members of the Lawson Wilkins Pediatric Endocrine Society were surveyed to establish the incidence of Nelson's syndrome in children treated with total bilateral adrenalectomy (TBA) for Cushing's disease. Thirty-one patients aged 10 mo to 16 yr had been treated with TBA for Cushing's disease; 1 had been treated with O,P'-dichlorodiphenyldichloroethane alone. Postadrenalectomy hyper-pigmentation was reported in 18 patients. Sella enlargement was detected in eight patients 1-5.5 yr (mean, 3 yr) post-TBA. Five of these patients developed pituitary adenomas. This incidence is higher than the adult figure of 10%-16%. (24 refs.)

- 78-0579 Mortality in a Lodging-House (Letter to Editor). (Eng) Mould, R. F. (Dept. Physics, Westminster Hosp., London SW1, England); Wrighton, K.; Pickup, D. S. *Lancet* 2(8049): 1180-1181; 1977.

An investigation of the high lung cancer mortality rate in a single municipal ward (population 5,000) of Liverpool revealed that a boardinghouse for men accounted for 10/47 cancer deaths in the period 1969-1976. In the same period, deaths at the boardinghouse accounted for 23% of deaths from all causes in the ward, 31% of deaths from chronic bronchitis, and 78% of deaths from pulmonary tuberculosis. (2 refs.)

- 78-0580 Comparative Epidemiology of Cancers of the United States and Japan. (Eng) Wynder, E. L. (Div. Epidemiology, American Health Foundation, 1370 Ave. of Americas, New York, NY 10019); Hirayama, T. *Prev Med* 6(4): 567-594; 1977.

A comparative epidemiological survey of the US white population and the general Japanese populations was made to determine whether differences in cancer incidence are related to specific environmental differences. Although malignant

neoplasms are the second leading cause of death in the US and Japan, there is a wide variance in rates for particular sites. A major difference is seen for cancer of the prostate, colon, buccal cavity, skin, lungs, and urinary bladder and leukemia, for which US men display higher death rates. Japanese men and women exhibit higher mortality rates for cancer of the stomach, esophagus, and liver. US women have greater mortality from breast and uterine cancer. In both countries death rates for cancer of the trachea, bronchus, and lung are increasing. Death rates for cancer of the prostate, bladder, and intestine are increasing in Japan and decreasing in the US. Japanese rates are approaching those for US whites. The consumption of cigarettes and dietary fats is sharply increasing in Japan. Environmental factors and dietary and social habits play an important role in the development of chronic diseases. (70 refs.)

- 78-0581 Cancer Mortality Rates and Drinking Water Quality in the Ohio River Valley Basin (Meeting Abstract). (Eng) Salg, J. A. (Univ. North Carolina Chapel Hill, Chapel Hill, NC). *Diss Abstr Int [B]* 38(6): 260B; 1977. (no refs.)

- 78-0582 Analysis of Smoke and Smoked Foods. (Eng) Hamm, R. (Bundesanstalt für Fleischforschung, Kulmbach, W. Germany). *Pure Appl Chem* 49(11): 1651-1666; 1977.

Wood smoke for smoking foods contains over 300 substances, the most important of which are phenols, carbonyls, acids, furans, alcohols, esters, lactones and polycyclic aromatic hydrocarbons (PAH). The use of PAH and phenols is singled out for discussion, and methods for the analysis of these compounds are outlined. The PAH content of meats can be reduced by smoking them at lower temperatures, by filtering or cooling the smoke, and by removing the soot from the food. Liquid smoke, which varies in composition from mixture to mixture, permeates the food with the smoke components including PAH thus creating a larger potential hazard than conventional smoking procedures. Phenols contribute mainly to the flavor of smoked foods. Their amount and composition can be influenced by temperature and by the smoking technology. However, an increase in phenolic content does not necessarily mean an increase in PAH concentration. Methods for the isolation and determination of PAH and phenols are available, but the identification of specific compounds is more difficult. If key substances that reflect the toxicological properties of food could be identified, the identification and control of smoke components in food would be simplified. The advantages and disadvantages of the various additives are outlined. (117 refs.)



78-0583 **Alterations in the Growth and Permeability in Malignant Cell Transformation (Meeting Abstract).** (Fre) Vilarem, M. J. (Centre de Recherches sur les Proteines, 45 rue des Saints-Peres 75006 Paris, France); Jouanneau, J.; Bourrillon, R. *Biol Cellulaire* 30(1): 21a; 1977. (no refs.)

cells or tumor cells arrested in target organ vessels at the time of surgical removal of the primary tumor make little contribution to overall survival. Therapy should be directed to established micrometastases rather than to these residual cells. In addition, the success of systemic adjuvant therapy in which each micrometastatic foci can be assumed to be exposed to the same local dosage is dependent on micrometastasis size rather than number. (17 refs.)

78-0584 **Micrometastasis Therapy: Theoretical Concepts.** (Eng) Liotta, L. A. (Lab. Pathology, NCI, NIH, Bethesda, MD 20014); Saidel, G.; Kleinerman, J.; DeLisi, C. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Sarattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 85-492; 1977.

Previously developed models of metastasis were applied to the systemic therapy of micrometastases, with particular emphasis on factors that determine the critical time period when micrometastases are first initiated. The mathematical model used describes the dynamics of tumor cell arrival in a target organ and the subsequent initiation and growth of metastatic foci. It was tested by applying it to a transplantable, poorly immunogenic murine fibrosarcoma that metastasizes to the lungs. Analysis of the model led to the conclusion that the initiation of micrometastatic foci can be modeled as a Poisson process. During the growth of a transplanted tumor, there exists a critical time period when the probability that no micrometastases exist rapidly decays to zero. The timing and type of this critical period are determined by the rate at which tumor cells are released from the tumor and arrest in the target organ and by survival parameters for arrested tumor cells. The small number of residual circulating tumor

*See also:*

\*(Rev.): 78-0003, 78-0004, 78-0005, 78-0006, 78-0007, 78-0009, 78-0012, 78-0013, 78-0014, 78-0016, 78-0018, 78-0024, 78-0025, 78-0027, 78-0034, 78-0035, 78-0036, 78-0039, 78-0040, 78-0041, 78-0043, 78-0044, 78-0045, 78-0047, 78-0048, 78-0049, 78-0050, 78-0052, 78-0055, 78-0056, 78-0059, 78-0060, 78-0062, 78-0067, 78-0069, 78-0070, 78-0071, 78-0102, 78-0103, 78-0104, 78-0105, 78-0107, 78-0111, 78-0112, 78-0113, 78-0114.

\*(Chem.): 78-0123, 78-0130, 78-0166, 78-0172, 78-0177, 78-0224, 78-0225, 78-0231, 78-0253, 78-0256, 78-0262, 78-0293, 78-0295.

\*(Viral): 78-0364, 78-0403.

\*(Immun.): 78-0440.

\*(Path.): 78-0455, 78-0459, 78-0460, 78-0476, 78-0478, 78-0503, 78-0510, 78-0512, 78-0521, 78-0526, 78-0528, 78-0531, 78-0532.



## MISCELLANEOUS

- 78-0585 **Plasmid Content and Tumor Initiation Complementation by *Agrobacterium tumefaciens* IIBNV6.** (Eng) Lippincott, B. B. (Dept. Biological Sciences, Northwestern Univ., Evanston, IL 60201); Margot, J. B.; Lippincott, J. A. *J Bacteriol* 132(3): 824-831; 1977.

Two avirulent strains, IIBNV6 and NT1, derived from virulent strains of *Agrobacterium tumefaciens*, were tested for their ability to enhance tumor initiation (complement) in *Phaseolus vulgaris* L. leaves upon coinoculation with tumorigenic strains. Strain NT1, cured of the *Agrobacterium* virulence plasmid, failed to complement when inoculated with its virulent parental strain or with other virulent strains. Strain IIBNV6, however, complemented with all virulent strains tested. Attachment to host wound sites by strain IIBNV6 and the virulent strain was essential for this effect. Inoculation of the tumorigenic strain at different times on leaves previously inoculated with IIBNV6 showed that the capacity to complement is lost between 4 and 8 hr after IIBNV6 inoculation. The rate of tumor appearance obtained with an inoculum containing IIBNV6 and a virulent auxotrophic strain was characteristic of the appearance rate obtained with prototrophic bacteria. Evidence is summarized that suggests that strain IIBNV6 can induce tumors when supplied with a substance produced or induced by a virulent bacterium at a separate site. A DNA plasmid about 40% the size of the *Agrobacterium* virulence plasmid was obtained from strain IIBNV6. It is proposed that this plasmid accounts for the ability of strain IIBNV6 to complement and that it contains part of the genetic information necessary for tumor initiation. (19 refs.)

- 78-0586 **Mutants of *Agrobacterium tumefaciens* with Temperature Sensitivity in Respect to Their Tumor Inducing Ability.** (Eng) Schilde-Rentschler, L. (Max-Planck-Institut für Biologie, Corrensstrasse 45, D-7400 Tübingen, W. Germany); Gordon, M. P.; Saiki, R.; Melchers, G. *Mol Gen Genet* 155(3): 235-239; 1977.

The isolation of six *Agrobacterium tumefaciens* mutants that induce tumors at 22 C but not at 28 C is reported. This sensitivity was not caused by an obvious metabolic defect. At the nonpermissive temperature, the mutants showed the same growth rates as wild-type mutants. The tumors induced by the mutants grew without the addition of hormones at both 22 and 28 C. Thus, the mutants were temperature-sensitive with respect to tumor-inducing ability but not maintenance of tumor phenotype. (20 refs.)

- 78-0587 **Studies on the Bacteriophage PS8 of *Agrobacterium tumefaciens* (Smith and Townsend).** (Eng) Knopf, U. C. (Carnegie Institution Washington, Dept. Plant Biology, Stanford, CA 94305). *Microbios* 17(70): 231-233; 1977.

These preliminary studies suggest that the DNA of *Agrobacterium tumefaciens* bacteriophage PS8 can exist in circles and that it has cohesive ends like the DNA of bacteriophage lambda. The PS8 DNA has a buoyant density of 1.716 cm<sup>3</sup>/g, a guanine-cytosine content of 57%, and a mol wt of 38.8 x 10<sup>6</sup> daltons. (23 refs.)

- 78-0588 **Depurination Decreases Fidelity of DNA Synthesis In Vitro.** (Eng) Shearman, C. W. (Institute for Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Loeb, L. A. *Nature* 270(5637): 537-538; 1977.

The effect of depurination of DNA on the fidelity of DNA synthesis in vitro was investigated using poly d(A-T) and an myeloblastosis virus DNA polymerase. The fidelity of DNA synthesis was decreased following depurination of the template. Incorporation of non-complementary nucleotides occurred randomly. Preliminary experiments indicate that these results hold for other templates and polymerases. A similar event in vivo could result from chemical carcinogens and lead to mutations or carcinogenesis. (13 refs.)

- 78-0589 **A Critical Comparison of Commonly Used Procedures for the Assay of Terminal Deoxynucleotidyl Transferase in Crude Tissue Extracts.** (Eng) O'Connor, M. S. (Dept. Biochemistry, Univ. Kentucky, Lexington, KY 40506). *Nucleic Acids Res* 4(12): 4305-4312; 1977.

Terminal deoxynucleotidyl transferase (TdT) is a non-template-directed DNA polymerase normally found in vertebrate thymus and bone marrow. Although quantitative TdT assays are widely used in the differential diagnosis of acute leukemias, clinical specimens of blood and bone marrow often contain  $\leq 10^7$  cells. A rapid, specific assay is described that can detect TdT at  $< 1$  unit/ $10^8$  cells in crude cell extracts. (17 refs.)



**78-0590 Purification, Biochemical Characterization and Serological Analysis of Cellular Deoxyribonucleic Acid Polymerases and a Reverse Transcriptase from Spleen of a Patient with Myelofibrotic Syndrome.** (Eng) Chandra, P. (Gustav-Embsden-Zentrum der Biologischen Chemie, Abteilung für Molekular-biologie der Universität Frankfurt/Main, Theodor-Stern-Kai 7, 6 Frankfurt/Main D, W. Germany); *Biochem J* 167(3): 513-524 167(3): 513-524; 1977.

The DNA polymerases and reverse transcriptase (RT) from the spleen of a 2.5-yr-old girl with osteomyelofibrosis were isolated and characterized. The specific requirements with respect to bivalent cations and template-primers for DNA polymerase  $\alpha$ , DNA polymerase  $\beta$ , DNA polymerase  $\gamma$ , and RT are reported. According to sedimentation velocity measurements, the mol wts of enzymes are 150,000, 40,000, 100,000 and 70,000 daltons, respectively. Serological studies indicated that the RRT from human spleen is antigenically related to the RT from simian sarcoma virus and gibbon-ape leukemia virus. This is the first DNA polymerase from human malignant tissue that meets the biochemical and immunological criteria of RT. Since another enzyme meeting these criteria was previously isolated from human leukemic cells, it is interesting that the girl in this study developed acute myelogenous leukemia 3 wk after surgery. This enzyme may have a prognostic role in human malignancy. (41 refs.)

**78-0591 The Study of Poly(A)-containing RNA of Lymphomatous Baboons.** (Eng) Djatchenko, A. G. (Inst. Experimental Pathology and Therapy, Acad. Medical Sciences USSR, P. B. 66, Gora Trapetziya, Sukhumi, USSR); *Archaja, I. I.; Berija, L. J. Exp Pathol (Jena)* 14(1/2): 65-68; 1977.

The content of messenger RNA (mRNA) particularly that of poly(A)-containing mRNA, was determined in the livers and spleens of lymphomatous baboons (*Papio hamadryas*). Poly(A)-RNA made up 8.04% of the nuclear mRNA of control livers compared to 22.1% in lymphomatous livers. The total poly(A)-RNA in the control livers contained about 1.1% poly(A)-RNA, the lymphomatous livers 31.1%; the total poly(A)-RNA of control spleens contained about 19.3% poly(A)-RNA, the lymphomatous spleens 47.6%. According to a hybridization-competition assay, the difference in hybridizable RNA's from normal and neoplastic baboons was the result of additional species of hybridizable mRNA in the total RNA pool in lymphomatous baboon spleen cells. Certain RNA species in the mRNA of malignant tissues were absent from RNA preparations of normal tissues. These findings suggest that transformation influences only the control of transcription, and not the total volume of genetic information. Synthesis of new mRNA molecules leads to alteration of the phenotype of transformed cells. (11 refs.)

**78-0592 Defective Transport of Thymidine by Cultured Cells Resistant to 5-Bromodeoxyuridine.** (Eng) Lynch, T. P. (Cancer Res. Unit, McEachern Lab., Univ. Alberta, Edmonton, Alberta, Canada T6G 2H7); Cass, C. E.; Paterson, A. R. *J Supramol Struct* 6 (3): 363-374; 1977.

HeLa S33 cells resistant to 5-bromo-2'-deoxyuridine (BUdR) were isolated in an attempt to obtain variants with defects in the membrane transport mechanism for thymidine. During selection, the cells were initially grown in medium containing 15  $\mu$ M BUdR; the concentration was gradually increased to 100  $\mu$ M. BUdR-resistant HeLa/B5 cells were isolated that contained thymidine kinase levels comparable to those of HeLa/0 cells; however, thymidine uptake rates were significantly lower in the former. HeLa/B5 cells were also resistant to 5-fluoro-2'-deoxyuridine (FUdR); both lines were equally sensitive to 5-fluorouracil, suggesting that the HeLa/B5 resistance was due to altered nucleoside uptake or metabolism. A comparison of labeled uptake indicated that the BUdR/FUdR resistance was due to impaired uptake of these agents. Thymidine kinase content and properties were similar in HeLa/B5 and parental lines, indicating that changes in enzyme activity was not responsible for the thymidine resistance of HeLa/B5 cells. Km values for thymidine, BUdR, and FUdR uptake were significantly higher in HeLa/B5 cells than in parental cells; adenosine uptake was unaffected. Furthermore, HeLa/B5 cells were less responsive than HeLa/0 cells to thymidine uptake inhibition by nitrobenzylthioinosine (NBMPR); the concentration required to reduce thymidine uptake to 50% of control values was 800 times higher than that reported for HeLa/0 cells. However, both cell lines had a similar number of NBMPR binding sites. The results indicate that the resistance of HeLa/B5 cells to BUdR and FUdR is due to a defect in their thymidine transport function. (34 refs.)

**78-0593 Transfer of Anchorage Independence by Isolated Metaphase Chromosomes in Hamster Cells.** (Eng) Spandidos, D. A. (Dept. Medical Genetics, Univ. Toronto, Toronto, Ontario, M5S 1A8, Canada); Siminovitch, L. *Cell* 12(3): 675-682; 1977.

The ability of Chinese hamster ovary (CHO) cells to transfer the property of being able to grow on agar (aga+) or to show anchorage independence to a baby hamster kidney cell line (BHK21/13) was investigated. CHO metaphase chromosomes were isolated, and  $5 \times 10^6$  cell equivalents were added to  $2 \times 10^6$  BHK cells. Growth in 0.5% or 1.0% agar resulted in approx  $2 \times 10^5$  colonies per plate; BHK cells alone produced only about  $2 \times 10^6$  colonies/plate, indicating that most of the former colonies were transformants. Repetition of the experiment using CHO donor cells and CHLRFStran4 recipients (a line derived by rescue of senescent Chinese hamster lung cells by transfer of CHO metaphase chromosomes) on 1% agar resulted in  $5 \times 10^6$  colonies per plate compared to no colonies when just the recipient cell was cultured. Karyotypic analyses indicated that the chromosome number



after each transfer was characteristic of the recipient cells. The transferred trait was found to be stable. Sucrose gradient centrifugation revealed that the aga+ marker was located in fraction A metaphase chromosomes; fractions B and C were similar to control cultures in which no chromosomes were transferred. The phenotypic trait of concanavalin A agglutinability, which is associated with aga+, was also transferred with the aga+ trait. Injection of 10<sup>3</sup> BHKaga+ cells into Syrian hamsters resulted in palpable tumors; 10<sup>7</sup> BHK21/13 cells were necessary to produce tumors, and these probably resulted from the low residual frequency of aga+ in the colonies. Tests with transformed CHO cells in Chinese hamsters gave similar results. Tumorigenicity apparently is associated with the aga+ characteristic. (39 refs.)

- 78-0594 Essential Role of Surface-bound Chemoattractant in Leukocyte Migration.** (Eng) Dierich, M. P. (Inst. Medical Microbiology, Johannes Gutenberg-Univ. Mainz, Augustusplatz, Mainz, W. Germany); Wilhelmi, D.; Till, G. *Nature* 270(5635): 351-352; 1977.

The nature of the chemoattractant response of guinea pig peritoneal granulocytes to casein was investigated by incubating granulocytes in compartments with casein or Hanks's balanced salt solution (HBSS) on filters that had been incubated on casein or HBSS. With casein concentrations of approx 3 mg/ml, almost identical migration distances were obtained whether the filters were preincubated in casein (first set) and used without further addition of casein, or whether the filters were initially free of casein (second set) and used in the test by adding casein to the compartment. At concentrations of 0.5 and 1 mg/ml, granulocytes in the first set of filters migrated longer distances than those in the second. With concentrations > 3 mg/ml, the first set of filters showed a slight increase in migration distance but the second set showed a continuous decrease of migration that was parallel to the increase in casein concentration. This reduction distance can only be attributed to casein not bound to the substratum. These results suggest that filter-bound casein promotes casein-induced WBC migration and that casein in free solution may be inhibitory. (12 refs.)

- 78-0595 Growth Stimulating Activity in Bovine Pituitary Extract Specific for a Rat Mammary Carcinoma Cell Line.** (Eng) Kano-Sueoka, T. (Dept. Molecular, Cellular and Developmental Biology, Univ. Colorado, Boulder, CO 80309); Campbell, G. R.; Gerber, M. *J Cell Physiol* 93(3): 417-424; 1977.

A growth factor (MGF) found in bovine pituitary extract that is specific for 64-24 rat mammary carcinoma cells was isolated and characterized. Using the growth rate in 10% fetal calf serum as unity, MGF in phosphate-buffered saline increased the relative growth (ratio of cell count of a sample plate to

that of a 10% calf serum plate) to 24.5 when the total extract was used. This decreased to 5.5 with the < 10,000-dalton fraction. When the crude extract was prepared in 0.075 M acetic acid, the relative growth in the < 10,000-dalton fraction was 44.6 while that in total extract was 62.5. These findings indicated that MGF was < 10,000 daltons, and according to fractionation techniques, it has a mol wt of 1,500-2,000 daltons. The isoelectric point of the protein is pH 3.8-4.0, and the UV absorption spectra is typical for a polypeptide that does not contain any aromatic amino acids. MGF is relatively heat-stable: its activity is reduced by about 30% after boiling for 10 min, but there is little change when it is kept at 70°C for 10 min. Preliminary results indicate that MGF contains only about 10 amino acids. (12 refs.)

- 78-0596 Cells on Stems.** (Eng) Desforges, J. F. (No affiliation given). *New Engl J Med* 298(2): 10; 1978.

The possibility that fetal RBC are involved in the differentiation of the erythroid stem cell from a pluripotent precursor is discussed, together with the significance of increased H<sub>2</sub>F production in B-chain genetic diseases such as sickle cell anemia and thalassemia. (5 refs.)

- 78-0597 The Correlation Between Morphological Appearance and Biological Behavior of Proliferative Hepatic Nodules in the Mouse (Meeting Abstract)** (Eng) Roth, R. N. (Albany Medical Coll., Union Univ., NY). *Diss Abstr Int [B]* 38(5): 2128B; 1977. (no refs.)

- 78-0598 Endo- and Exoglycosidases in an Experimental Rat Osteosarcoma.** (Eng) Harris, P. A. (Randmond Purves Res. Labs., Univ. Sydney, Royal North Shore Hosp. Sydney, St. Leonards, New South Wales, 2065, Australia); Stephens, R. W.; Ghosh, P.; Taylor, T. K. *Aust J Exp Biol Med Sci* 55(pt 4): 363-370; 1977.

The ability of homogenates of a <sup>32</sup>P-induced osteosarcoma DA rats to degrade polysaccharides in the intercellular matrix was investigated. Tumor homogenates readily degraded hyaluronic acid, chondroitin-6-sulfate, and chondroitin sulfate at pH 4.0; no degradation of glycosaminoglycans occurred at pH 7.0. Exoglycans contributed to 51% of the degradation, hyaluronidase to the remainder. High levels of exoglycosidases  $\beta$ -glucuronidase and  $\beta$ -acetylglucosaminidase were found in the tumor homogenates. When osteosarcoma cells were cultured in a serum-free medium, significant levels of  $\beta$ -glucuronidase and  $\beta$ -acetylglucosaminidase, but not hyaluronidase, were found 48 hr later. A comparison of the tumor enzyme values with those of the surrounding tissue gave markedly lower activities for the exoglycosidases and similar levels for hyaluronidase; e



cosidase activity/mg tissue protein or DNA is significant-elevated in the tumors compared to neonatal bones, but neonatal bone protein contained significantly more aluronidase than tumor. (28 refs.)

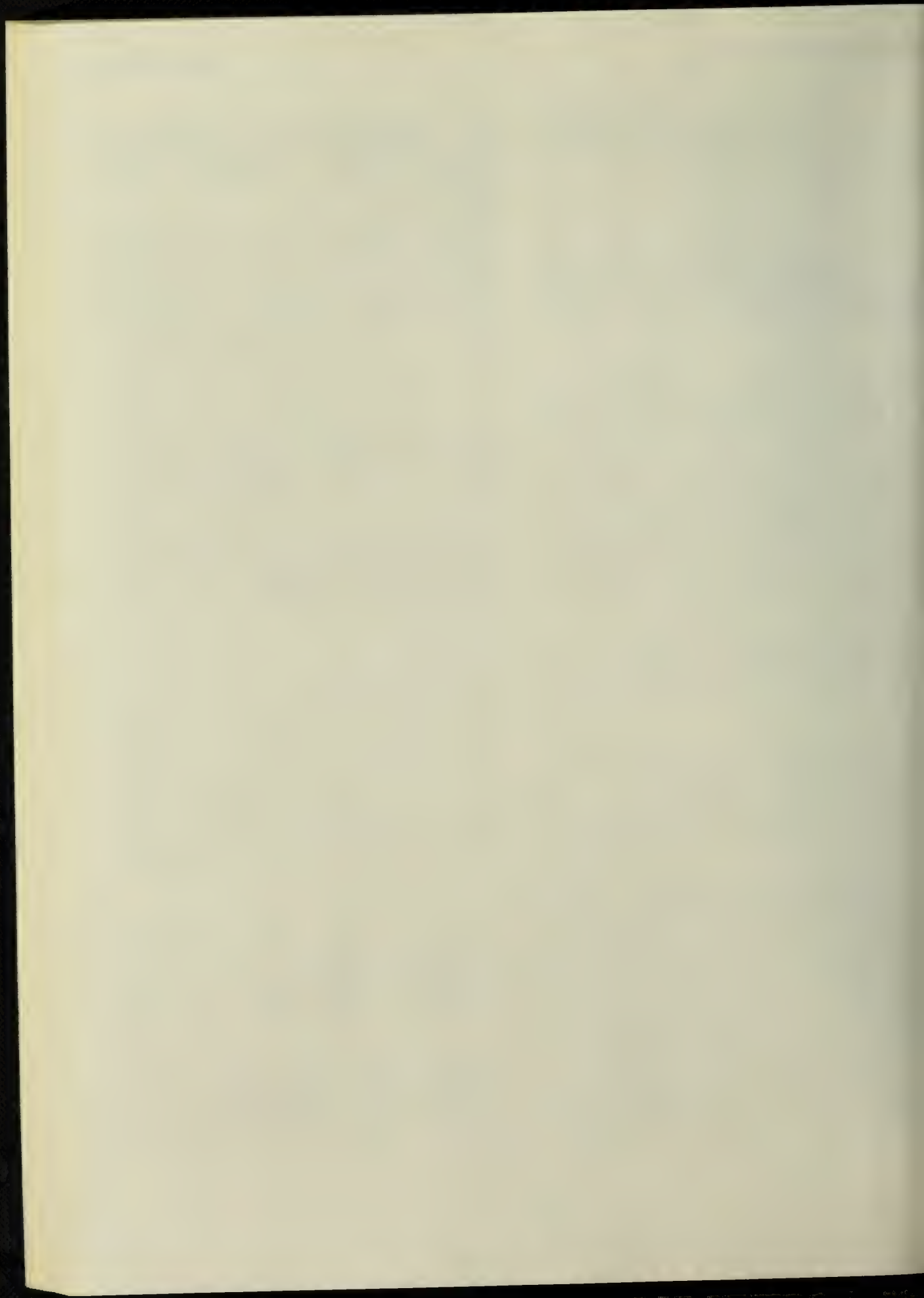
78-0599 **Increased CTP Synthetase Activity in Cancer Cells.** (Eng) Williams, J. C. (Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianapolis, IN 46202); Kizaki, H.; Weber, G.; Morris, H. P. *Nature* 1(5640): 71-73; 1978.

Cytosine triphosphate synthetase (CTPS) activity was investigated in liver extracts of ACI/N and Buffalo inbred rats, Fischer rats, and in several rat hepatomas with varying growth rates. Specific CTPS activity in normal rat liver ranged from 4 to 6 nanomoles/mg protein. This activity was increased 1.8-3.6 times in the slow- and medium-growth hepatomas and 4.6 to 11.2 times in the rapidly growing hepatomas. CTPS activity was increased twofold in 24-hr regenerating liver, compared to sham-operated controls. Enzyme activity in 5-day-old rats was 31% of that in normal adults; therefore, the increases are not linked with differentiation. It is suggested that the high CTPS activity in the hepatomas is associated with the reprogramming of gene expression during malignant transformation and progression. (23 refs.)

78-0600 **Characterization of a Major Fibroblast Cell Surface Glycoprotein.** (Eng) Yamada, K. M. (Lab. Molecular Biology, NCI, NIH, Bethesda, MD 20014); Schlesinger, D. H.; Kennedy, D. W.; Pastan, I. *Biochemistry* 16(25): 5552-5559; 1977.

The isolation and partial characterization of CSP, the major glycoprotein on the surface of chick embryo fibroblasts, are reported. CSP was insoluble in isotonic solutions at pH 7 even in the presence of nonionic detergents or 0.1 M EDTA, or at high ionic strength. It was soluble at high pH ( $\text{pH} \geq 11$ ) or low pH ( $\text{pH} \leq 3$ ) and in 8 M urea or 6 M guanidine-HCl. When nonreduced CSP was chromatographed on Sepharose CL 4B at pH 11 and analyzed by electrophoresis in sodium dodecyl sulfate gels, it consisted of a major species of disulfide-linked multimer that is probably a dimer, plus lesser amounts of monomer and larger complexes. Upon reduction with or without alkylation, all these CSP species migrate as the monomer. The Stokes radius of the CSP monomer estimated by gel filtration was 110 Å. The CSP of chick fibroblast cell homogenates migrated as multimers prior to disulfide reduction and as the monomer after reduction. CSP did not contain a preponderance of any particular amino acid class and it had only 20% hydrophobic residues. The amino terminus was blocked and was not removed by pyroglutamate aminopeptidase. The glycoprotein contained 5%-6% carbohydrates, including N-acetylglucosamine, mannose, galactose, sialic acid, and glucose. (60 refs.)







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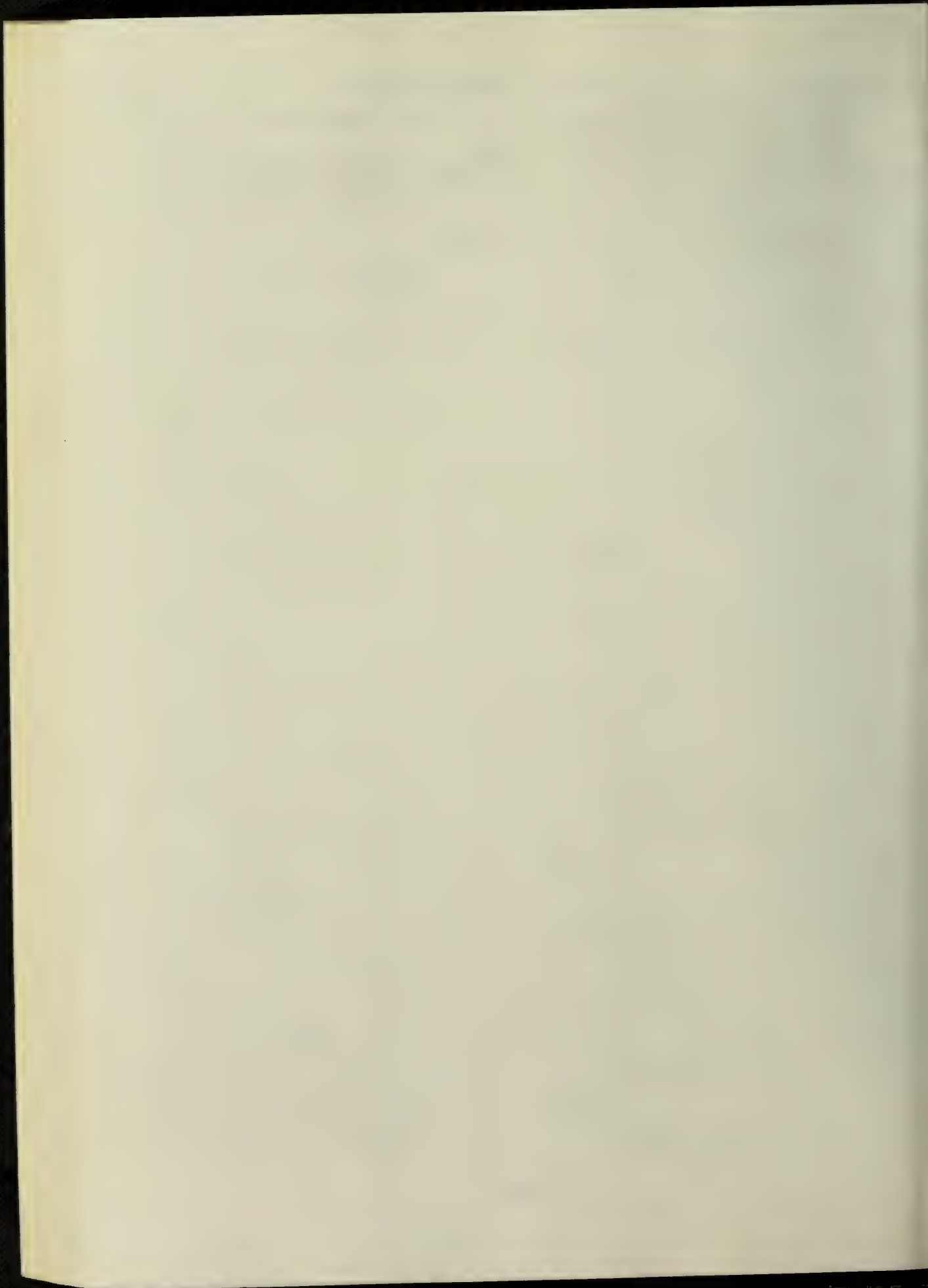
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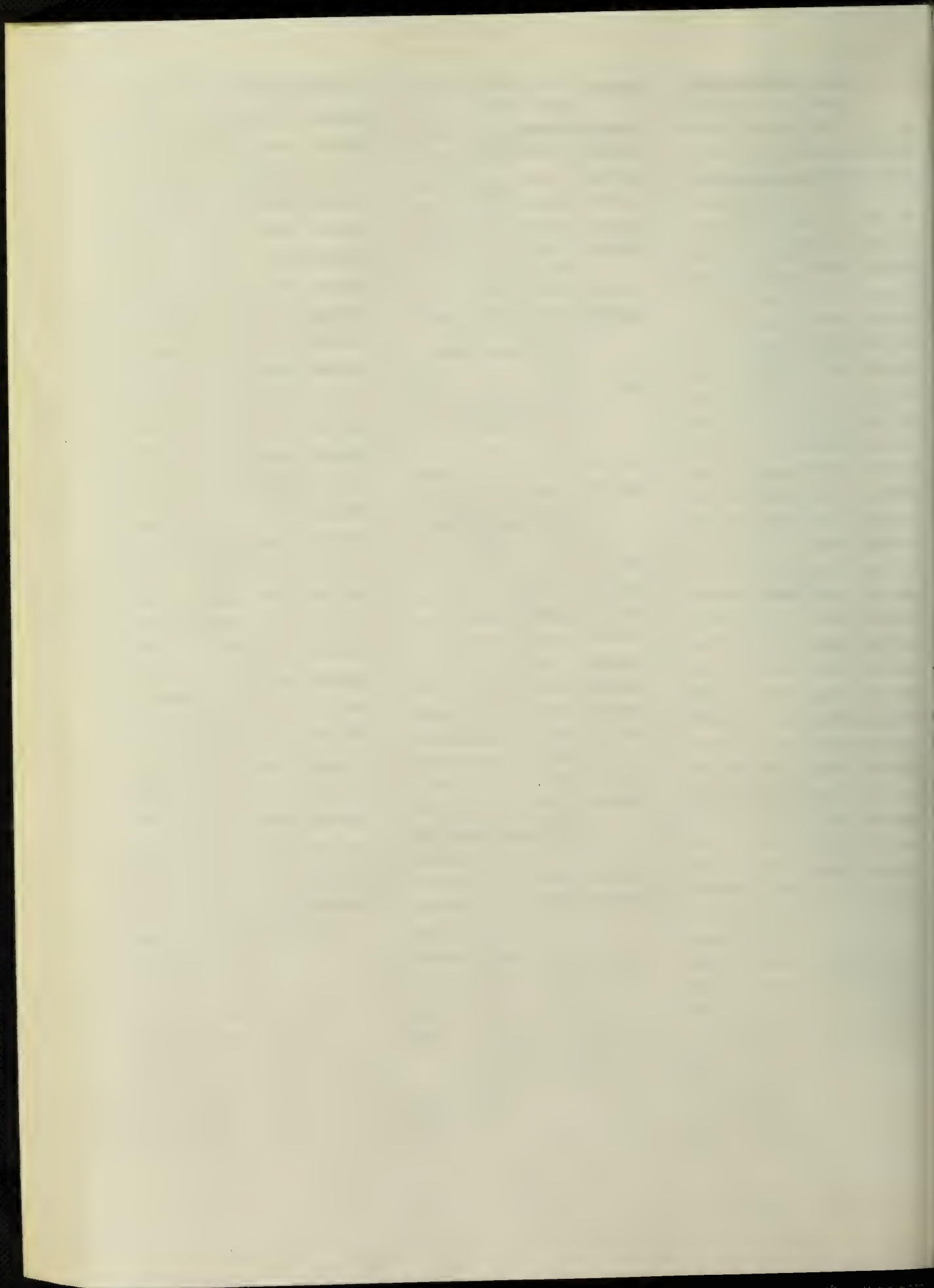


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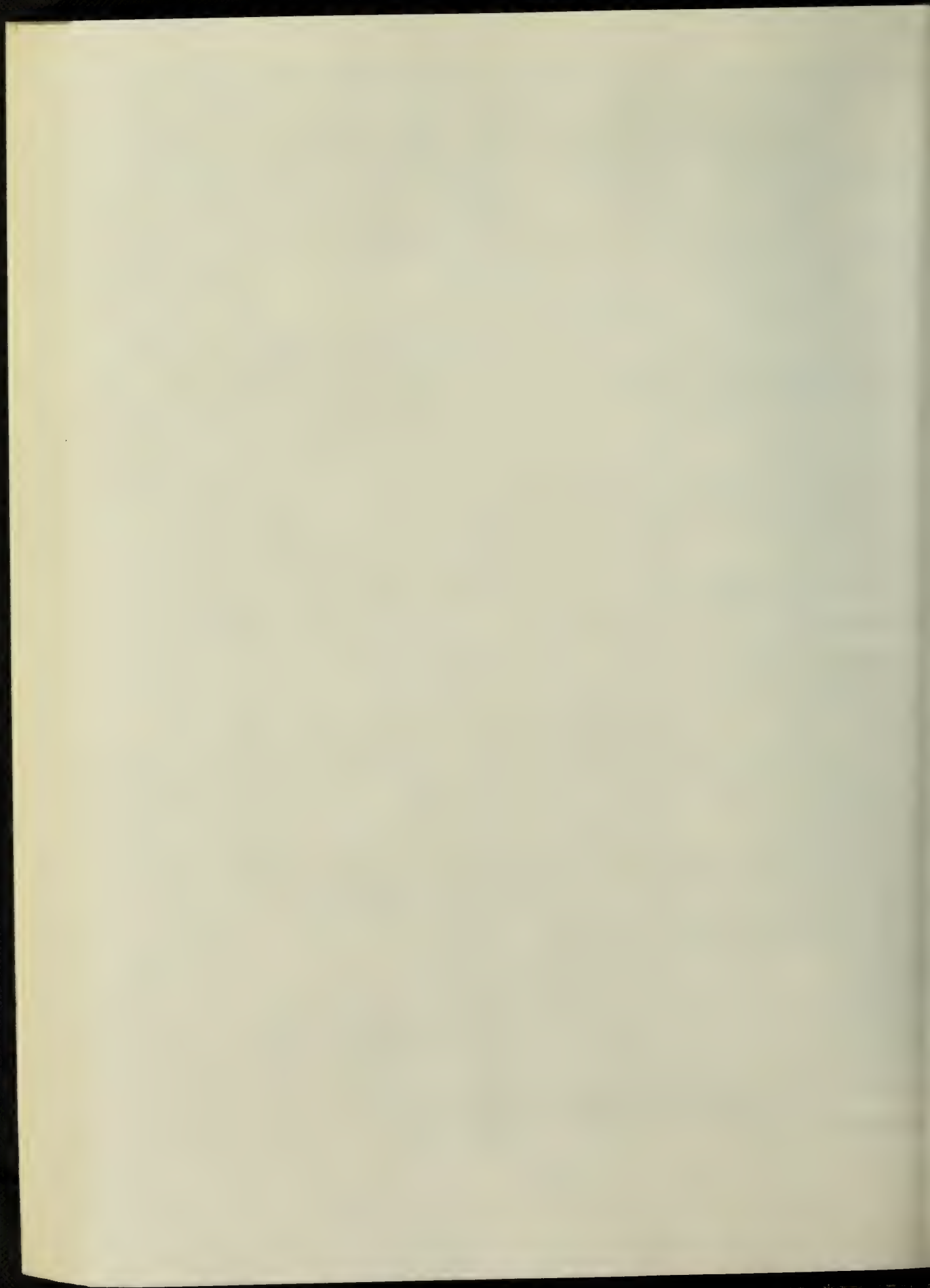
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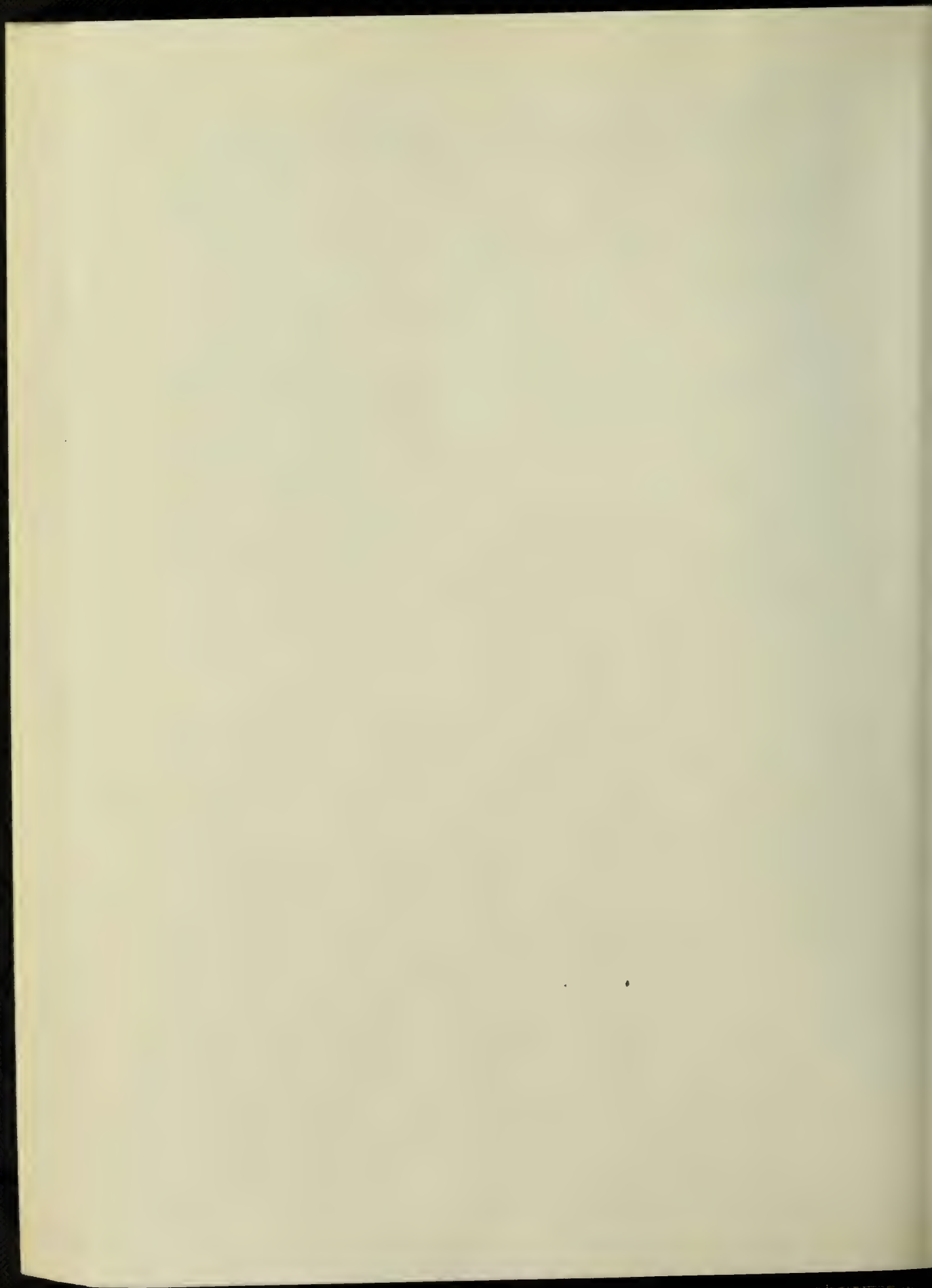
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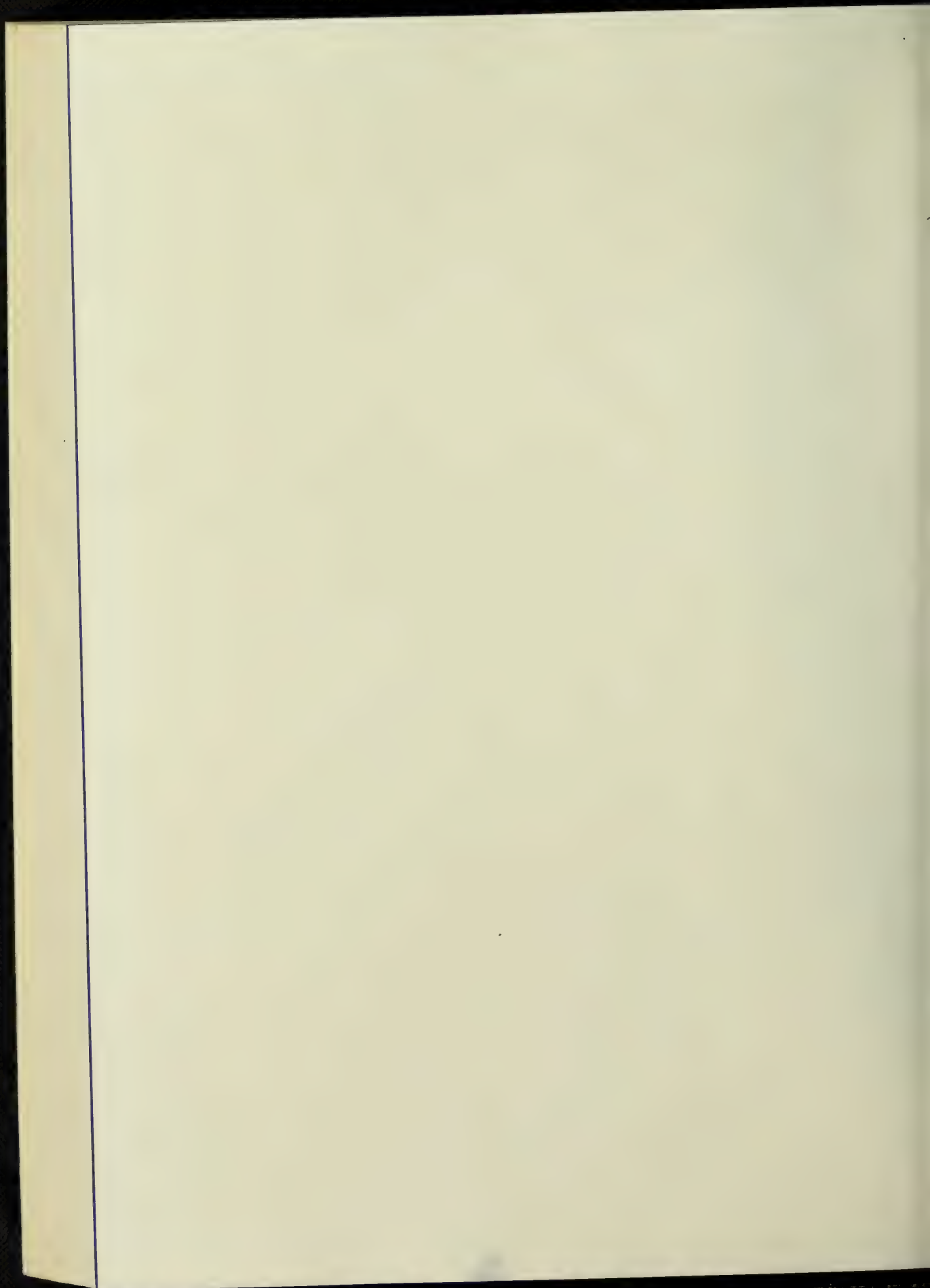
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## **EDITOR**

**GEORGE P. STUDZINSKI, M.D., Ph.D.**  
COLLEGE OF MEDICINE AND DENTISTRY  
OF NEW JERSEY, NEWARK

## **ASSOCIATE EDITOR**

**JUSSI J. SAUKKONEN, M.D.**  
JEFFERSON MEDICAL COLLEGE  
PHILADELPHIA

## **NCI STAFF CONSULTANTS**

**ELIZABETH WEISBURGER, Ph.D.**  
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**BRUCE H. KLEINSTEIN, Ph.D., J.D., Assistant Director, Biomedical Projects**

**RUTHANN E. AUCHINLECK, Managing Editor**

**The Franklin Research Center**  
**The Benjamin Franklin Parkway, Philadelphia, Pennsylvania 19103**



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# CARCINOGENESIS ABSTRACTS

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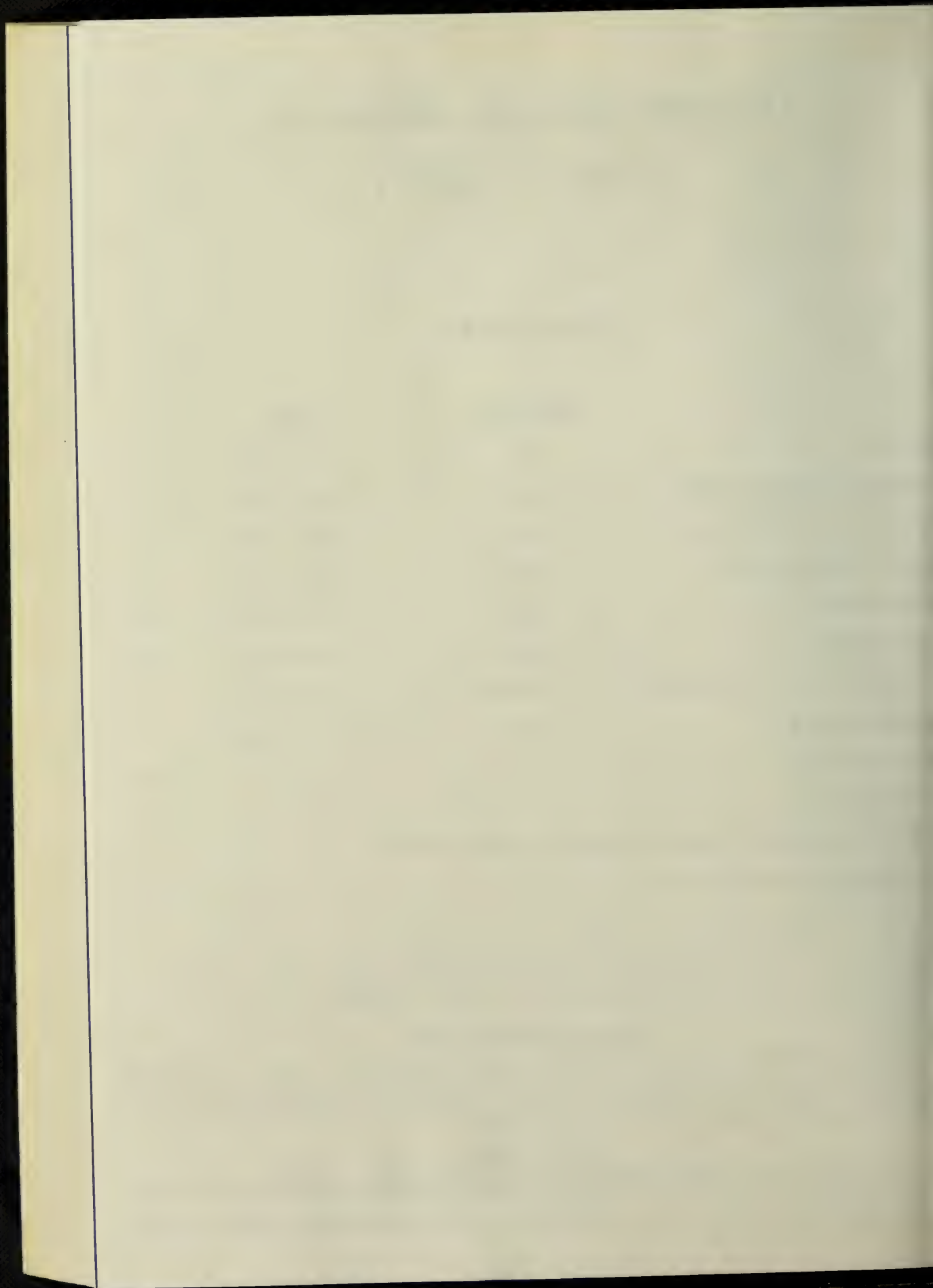
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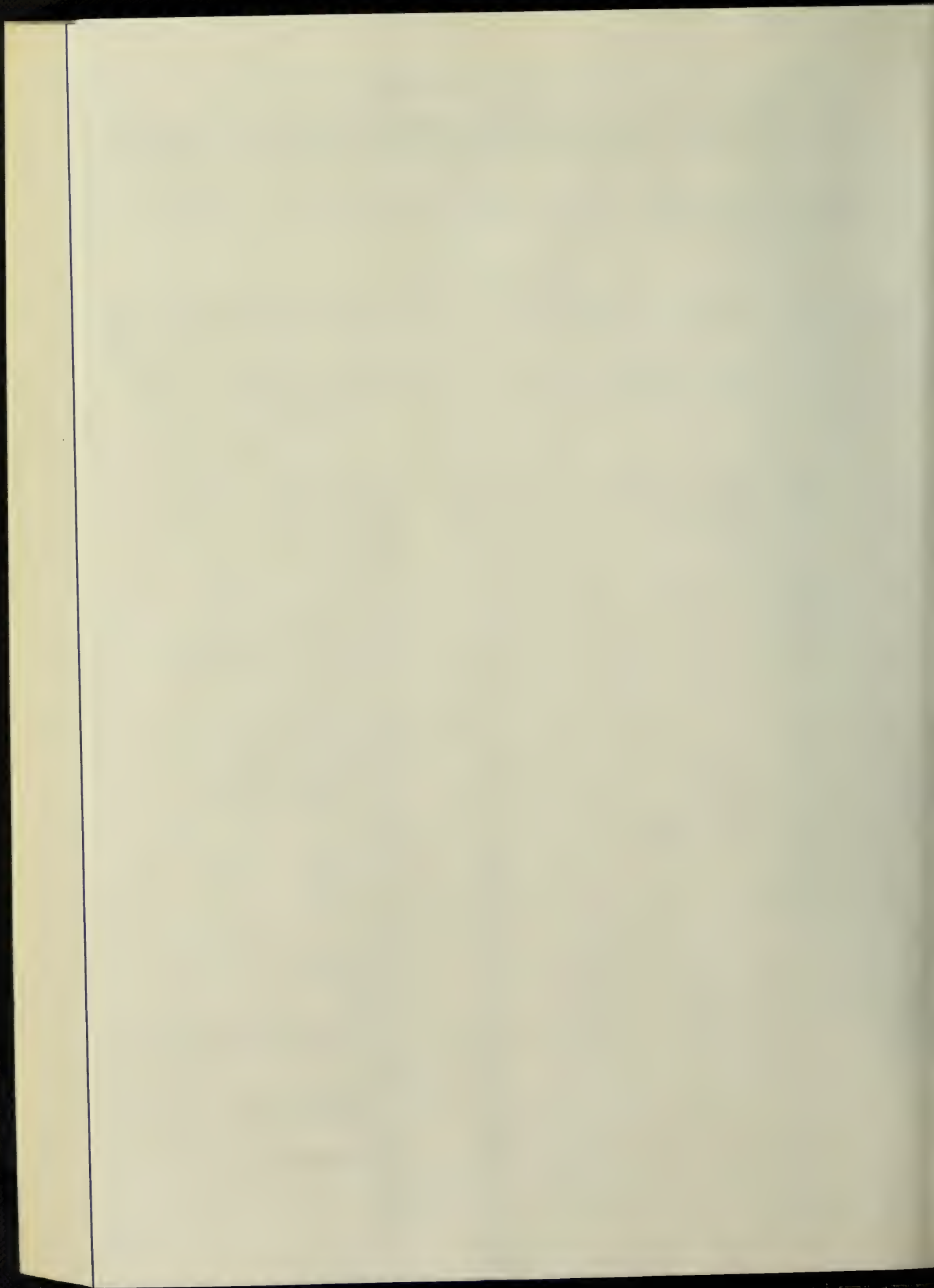
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**ABBREVIATIONS** used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED <sub>50</sub>	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO <sub>2</sub>	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD <sub>50</sub>	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD <sub>50</sub>	median lethal dose		
M	molar		
μM	micromolar		







## REVIEW

- 78-0601 The Molecular Site of Benzene Toxicity.** (Eng) Freedman, M. L. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY). *J Toxicol Environ Health* (Suppl. 2): 37-43; 1977.

Data suggesting various molecular sites and mechanisms of benzene toxicity are presented. The proposed mechanisms include the following: inhibition and disturbance of both DNA and RNA synthesis, translation of RNA, inhibition of initiation of translation, inhibition of initiation with normal elongation and release, and inhibition of heme synthesis either at or before 4-aminolevulinic acid synthetase. The primary effect of benzene is on differentiated cells and not stem cells. There is also evidence that benzene, lead, and alcohol have additive effects on the inhibition of protein and heme synthesis. Further investigations of the interrelationships among heme synthesis, cyclic AMP, and pyridoxine metabolism might reveal some therapeutic implications in benzene-induced hematological toxicity. (refs)

- 78-0602 Experimental Benzene Intoxication.** (Eng) Leong, B. K. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY). *J Toxicol Environ Health* (Suppl. 2): 45-61; 1977.

A review of experiments on benzene toxicity is presented. The narcotic threshold concentration for inhalation in laboratory animals is approx 4,000 ppm, and concentrations > 10,000 ppm are generally fatal. Sc administration results in leukopenia; continued sc injections lead to lymphatic hypoplasia, fibrotic degeneration, erythroblastic hypoplasia, and severe hemolytic anemia. Both myeloid and lymphoid tissue are affected by benzene, but the former is more sensitive than the latter. Although there is no convincing evidence that benzene induces leukemia or solid tumors in laboratory animals, some forms of benzene intoxication result in hyperplasia of the bone marrow, with the occurrence of many bizarre cell species, some of which may be neoplastic. Damage to immunological mechanisms in benzene toxicity may then impair the immune surveillance response, resulting in the development of leukemia. Although there have been several reports of the embryonic and teratogenic effects of benzene, experiments on realistic exposure concentrations are lacking. Biochemical and histochemical studies have yet to reveal the exact mechanisms of benzene toxicity. (refs)

- 78-0603 Cytologic and Cytogenetic Effects of Benzene.** (Eng) Wolman, S. R. (Dept. Pathology, New

York Univ. Sch. Medicine, New York, NY). *J Toxicol Environ Health* (Suppl. 2): 63-68; 1977.

The best source of data on the cytologic and cytogenetic effects of benzene exposure comes from industrially exposed human populations. The largest number of recorded observations of nuclear damage pertain to chromosome alterations. Both numerical and structural chromosome aberrations have been described that could be interpreted as either toxic or mutational damage. A review of patients exposed to benzene for as long as 22 yr reveals diagnoses of acute intoxication, death with massive bleeding and extramedullary hematopoiesis, benzene leukemia, acute myeloid leukemia, acute erythroblastosis, erythroleukemia, acquired aplastic anemia, acute lymphoblastic leukemia, myelofibrosis, and chronic myelogenous leukemia. There is also ample evidence from experimental studies that chromosome aberrations, pancytopenia, and marrow aplasia can be induced by exposure to benzene. However, the mode of action of this chemical has yet to be identified. (refs)

- 78-0604 Hematotoxicity in Humans.** (Eng) Goldstein, B. D. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY). *J Toxicol Environ Health* (Suppl. 2): 69-105; 1977.

The hematotoxicity of benzene (BZ) in humans is reviewed. One consequence of prolonged BZ exposure is pancytopenia, a decrease in the various formed elements of the circulating blood. Although stem cell destruction is known to occur in this disorder, as evidenced by the aplastic bone marrows in BZ-exposed animals and humans, the presence of bone marrow hyperplasia in some patients suggests that either a failure of stem cell differentiation or a BZ-induced destruction of intermediate precursor cells may also be occurring. Leukemia, especially acute myelogenous leukemia, erythroleukemia, and myelomonocytic leukemia, can result from BZ exposure, but the incidence appears to be a small fraction of BZ-induced hematotoxicity. The mechanism by which BZ may result in leukemia is unknown. Other hematological diseases that may be associated with BZ exposure include paroxysmal nocturnal hemoglobinuria, myelofibrosis, myeloid metaplasia, and Hodgkin's disease, but the evidence is not convincing. Host factors that may be associated with BZ toxicity include hereditary factors, age, hematopoietic system status, and enzymes and intermediates in BZ metabolism. The easiest way of detecting BZ hematotoxicity is by regular cell counts, and these should be performed on workers exposed to the compound. (refs)



- 78-0605 **Benzene Metabolism.** (Eng) Rusch, G. M. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY); Leong, B. K.; Laskin, S. *J Toxicol Environ Health* (Suppl. 2): 23-36; 1977.

A review of benzene metabolism in humans and animals is presented. The metabolism appears to follow similar pathways in all species, with the major differences arising in the conjugation of the final metabolites. Species such as the pig show a preference for glucuronide formation, but humans and dogs show a preference for sulfate formation. With human and dogs, sulfonation is the predominant method of conjugation when exposure levels are low, and glucuronide formation takes place only when the sulfonation route is used heavily. In rats, the levels of sulfonating enzymes in the liver increase with age; this is accompanied by an increased resistance to benzene poisoning. Chronic benzene toxicity appears to be related to the levels of benzene metabolites present in the animal. Treatments that increase the rate of benzene metabolism, such as phenobarbital, also increase the rate of elimination of metabolites, thereby decreasing total exposure and the resulting toxicity. Treatments that decrease the metabolic rate, such as partial hepatectomy, cysteamine, and SKF 525A, decrease the level of metabolites and, in some cases, the chronic toxicity. However, none of these pretreatments alters acute toxicity. Tissue distribution patterns depend on the method of administration. The mechanism of benzene toxicity is unknown. (refs)

- 78-0606 **An Overview of Metal Carcinogenesis.** (Eng) Furst, A. (Inst. Chemical Biology, Univ. San Francisco, San Francisco, CA). *Adv Exp Med Biol* 91: 1-12; 1977.

Metals and their compounds that have been tested for carcinogenicity in animals are discussed. In the case of nickel and cadmium, both element and compounds appear to be active carcinogens. In contrast, lead is inactive as the free element but active in its acetate form. Potential carcinogens that require further testing in animals include chromates, zinc, cobalt, manganese, and selenium. Metals found to be noncarcinogenic for animals (eg, aluminum and copper) require reevaluation, since their effects may vary with different routes of administration or different species and strains. Proposed mechanisms of metal carcinogenesis are summarized with emphasis on nucleic acid-metal interactions. (81 refs.)

- 78-0607 **Carcinogenic Effects of Metals.** (Eng) Sunderman, F. W. (Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT 06032). *Fed Proc* 37(1): 40-46; 1978.

A review of the carcinogenicity of various metals in man and

experimental animals is presented. Inhalation of As has been linked to pulmonary carcinomas, lymphomas and leukemias, and dermal carcinomas; po exposure has been linked to dermal carcinomas and hepatic angiosarcomas. Workers exposed to Cd by inhalation have a higher than expected incidence of both lung and prostatic carcinomas. Cr inhalation has been linked to pulmonary carcinomas and, possibly, to gastrointestinal carcinomas. Ni inhalation has been linked to pulmonary, nasal/sinus, and laryngeal carcinomas and, possibly, to gastric and renal carcinomas and sarcomas. Be, Fe, and Pb workers have increased risks of pulmonary carcinoma, and injection of Fe-dextran complexes may be an etiologic agent in the development of sarcoma. In laboratory studies, osteosarcomas and carcinomas have been induced following Be exposure; sarcomas, leydiomas, and teratomas from Cd; sarcomas from Co; sarcomas and carcinomas from Cr; sarcomas from Fe; sarcomas and carcinomas from Ni; carcinomas from Pb; sarcomas from Ti; and carcinomas and teratomas from Zn. In vitro tissue culture systems, microbial mutagenicity tests, and the Sirover and Loeb technique could be used to assess the mutagenicity or carcinogenicity of metal compounds. However, the *Salmonella typhimurium* tests may not be suitable. (126 refs.)

- 78-0608 **Carcinogenicity of Nickel Subsulfide in Fischer Rats and Syrian Hamsters after Administration by Various Routes.** (Eng) Sunderman, F. W. (Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032); Maenza, R. M.; Alpass, P. R.; Mitchell, J. M.; Damjanov, I.; Goldblatt, P. J. *Adv Exp Med Biol* 91: 57-67; 1977.

The carcinogenicity of nickel subsulfide ( $\text{Ni}_3\text{S}_2$ ; NS) was investigated in 113 male Syrian LVG/LAK hamsters and 10: male albino Fischer 344 rats by five previously untested routes. One group of hamsters was inoculated im with a single dose of 5 or 10 mg NS. In another group, an NS-glycerol suspension was painted over the mucosa of each cheek pouch (1, 2, 5, or 10 mg 3 x/wk, for 18 or 36 wk). As positive controls, a third group was painted similarly with 0.1 ml of a 0.5% solution of 9,10-dimethyl-1,1-benzanthracene. NS induced rhabdomyosarcomas, fibrosarcomas, and undifferentiated sarcomas in 17/32 hamsters inoculated im, but it did not induce any malignant tumors of the cheek pouches, oral cavity, or gastrointestinal tract, despite total doses as large as 1.1 g. The rats were given single injections of NS im (1 mg), into the submaxillary gland (2.5 mg), into the liver (1 mg), and into the testis (10 mg). Tumors developed only in rats inoculated im (22/23) and intratesticularly (16/19). (3 refs)

- 78-0609 **Lung Tumor Response in Mice to Metals and Metal Salts.** (Eng) Shimkin, M. B. (Univ. California, San Diego, La Jolla, CA, 92093); Stoner, G. D.; Theiss, J. C. *Adv Exp Med Biol* 91: 85-91; 1977.



Investigations of the ability of metals and their salts to induce lung tumors in strain A mice are summarized. Of 13 metal salts, only lead subacetate, manganous sulfate, molybdenum oxide, and nickelous acetate significantly increased ( $p < 0.05$ ) the av number of lung tumors per mouse after 6-24 ip injections. In another experiment, single iv injections of arpyrite, chromite, quartz, and thorite did not produce lung tumors or enhance tumor induction by 3-methylcholanthrene (0.1 mg iv). Thus, the ores were neither carcinogenic nor cocarcinogenic. Possible reasons for the discrepancy between these results and those obtained in other studies of metal carcinogenesis are discussed. (8 refs.)

- 0610 **Cigarette Smoking and Cancer of the Lung: A Review.** (Eng) Kakvan, M. (Dept. Surgery, Baylor Coll. Medicine, Houston, TX 77030); Greenberg, S. D. *Med J* 60(12): 588-591, 606; 1977.

The relationship between the chemical composition of tobacco and lung cancer is reviewed together with the biological, pathological, and clinical aspects of cigarette smoking. Ten of the 18 hydrocarbons in cigarette smoke tar can induce carcinomas in animals. In man, the incidence of lung cancer increases with the mean number of puffs per cigarette, duration of smoking (pack-years), amount of smoking per day, and number of puffs taken toward the end of the cigarette. However, the anaplastic process induced by chronic smoking is reversible with the cessation of smoking. The feasibility of producing less-toxic cigarettes ( $< 20$  mg tar and 1 mg nicotine) is discussed. (51 refs.)

- 0611 **The Phenomena of Quality in the Smoke Curing Process.** (Eng) Tilgner, D. J. (Sopot, Poland). *Pure Appl Chem* 49(11): 1629-1638; 1977.

Smoke used to cure meats can be made free of polynuclear hydrocarbons, ie, benzo(a)pyrene, by a two-stage smoke-generation process. Other advances in smoke curing that have occurred over the past 25 yr are reviewed. (59 refs.)

- 0612 **The Effects of Smoking on Immunocompetence.** (Eng) Chretien, P. B. (Surgery Branch, NCI, Bethesda, MD 20014). In: *Head and Neck Cancer. State of the Art Conference. February 16, 17 and 18, 1976.* (St. Louis, MO: Laryngoscope): Vol.88, No.1, Part 2, Suppl. 8, pp. 11-1978.

Although the exact mechanism by which tobacco smoke initially increases cellular immunity is unknown, current data suggest an association among tobacco consumption, cellular immune depression, humoral antibodies to herpes simplex

virus-induced antigens, and malignant transformation. (no refs.)

- 78-0613 **Alcohol Consumption and Cellular Immunocompetence.** (Eng) Palmer, D. L. (2100 Ridgcrest Drive, SE, Albuquerque, NM). In: *Head and Neck Cancer. State of the Art Conference. February 16, 17 and 18, 1976.* (St. Louis, MO: Laryngoscope): Vol.88, No.1, Part 2, Suppl. 8, pp. 13-17; 1978.

Alcohol may depress cell-mediated immunity and thus increase the risk of cancer. There may be a direct cytotoxic effect with a more profound effect on the T cells, alcoholic cirrhosis may induce defects in lymphocyte-mediated immunity, and alcohol may depress cell-mediated immunity indirectly through malnutrition. (24 refs.)

- 78-0614 **A Biochemical Approach to the Etiology of Alcohol Related Cancers of the Head and Neck.** (Eng) McCoy, G. D. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY). In: *Head and Neck Cancer. State of the Art Conference. February 16, 17 and 18, 1976.* (St. Louis, MO: Laryngoscope): Vol. 88, No. 1, Part 2, Suppl. 8, pp. 59-62; 1978.

The following working hypothesis for the increased risk of oral, laryngeal, and esophageal cancer in heavy drinkers who smoke is proposed. Nutritional deficiencies (ie, in riboflavin and/or iron) in conjunction with chronic ethanol intake promote the accumulation of fatty acyl coenzyme A esters, which inhibit mitochondrial adenine nucleotide transport and result in decreased ATP synthesis. Now the cell must produce ATP by other pathways, such as glycolysis, to survive. This hyperplastic cell requires enhanced ribo- and deoxynucleotide biosynthesis, which requires enhanced hexose monophosphate shunt activity. The latter results in increased NADPH production. The metabolic activation of procarcinogens is increased by the availability of NADPH, and this enhanced rate of carcinogen production and the enhanced mitotic activity doom the hyperplastic cell to neoplastic conversion. Other studies have indicated that in the hamster, an ideal animal for studies on ethanol activity in the oral mucosa, cell-free extracts of cheek pouch epithelial lining have the enzymatic ability to oxidize both ethanol and acetaldehyde. (14 refs.)

- 78-0615 **Epidemiology of Aflatoxin Carcinogenesis.** (Eng) Shank, R. C. (Dept. Community and Environmental Medicine, Coll. Medicine, Univ. California at Irvine, Irvine, CA). In: *Environmental Cancer.* Kraybill, H. F.; Mehlman, M. A., eds. (New York: John Wiley & Sons):



Advances in Modern Toxicology, Vol. 3, 388 pp., 291-318; 1977.

Experimental and epidemiological evidence supporting a role for aflatoxin in the etiology of human liver cancer is reviewed. Aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) is the most potent hepatocarcinogen in experimental animals: all species tested develop liver carcinoma. Human liver contains enzymes capable of metabolizing AFB<sub>1</sub>, although the proximate carcinogen for AFB<sub>1</sub> has not yet been established. In Uganda and Swaziland, where there is extensive contamination of foodstuffs by aflatoxins, the incidence of human liver cancer is increased. Dose-response relationships for aflatoxin ingestion and human primary liver cancer have been observed in Kenya, Mozambique, and Thailand, and the relationships are in quantitative agreement in the three independent studies. Other factors, such as an attack of viral hepatitis, a chronically poor diet, cirrhosis, or parasitic infection, may interact with the aflatoxin to produce liver tumors. It is concluded that there is strong presumptive evidence that aflatoxin is a human carcinogen and that it is responsible, at least in part, for some of the primary liver cancers that develop in populations in Africa and Southwest Asia. (103 refs.)

- 78-0616 **Aflatoxin and Liver Cell Cancer.** (Eng) Linsell, C. A. (International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France); Peers, F. G. *Trans R Soc Trop Med Hyg* 71(6): 471-473; 1977.

Epidemiologic studies and cancer registry data linking dietary aflatoxin to liver cancer are summarized. The association has been observed in widely separated geographical areas in Thailand and Africa, with documented high levels of aflatoxin ingestion being paralleled by a high frequency of liver cancer. (18 refs.)

- 77-0617 **Ligandin, the Glutathione S-Transferase, and Chemically Induced Hepatocarcinogenesis: A Review.** (Eng) Smith, G. J. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140); Ohl, V. S.; Litwack, G. *Cancer Res* 37(1): 8-14; 1977.

The glutathione S-transferases are a major group of soluble liver proteins involved in the cellular detoxification of electrophilic compounds. Several of these transferases, in particular glutathione S-transferase B or ligandin, interact with chemical carcinogens in vivo. In this review, evidence is presented that ligandin and the other glutathione S-transferases reduce the susceptibility of the liver to carcinogenesis induced by aminoazo dyes, polycyclic aromatic hydrocarbons, and aromatic amines. Several possible mechanisms by which the

transferases reduce hepatocarcinogenesis are proposed. They increase the direct binding and detoxification of carcinogens by the transferase and the inactivation of steroids and other agents that indirectly stimulate carcinogen activation. (75 refs.)

- 78-0618 **The Effect of Carcinogenic Chemicals on Ascorbic Acid Metabolism.** (Eng) Lamb, E. (High River Inst. Theoretical Cancer Study, High River, Alberta, Canada); Loucks, E.; Hancock, R. L. *Eur J Drug Metab Pharmacokinet* 2(2): 51-61; 1977.

The effect of various carcinogens, including 3-methylcholanthrene, 3,4-benzpyrene, and 1,2,5,6-dibenzanthracene, on ascorbic acid metabolism in experimental animals is reviewed. The influence of hormones and studies with scorbutic animals are also included. Mechanisms explaining increases in the synthesis and excretion of ascorbic acid induced by carcinogens are summarized. (63 refs.)

- 78-0619 **Diethylstilbestrol Exposure In Utero.** (Eng) Newell, G. R. (Nat'l. Cancer Program, NCI, Bethesda, MD 20014). *South Med J* 70(12): 1459-1460; 1977.

In utero exposure to diethylstilbestrol (DES)-type hormone has been documented in two-thirds of the 300 cases of clear cell vaginal adenocarcinoma reported to a tumor registry. The diagnosis and management of these tumors and other abnormalities associated with DES exposure are summarized. (2 refs.)

- 78-0620 **Oestrogens and Uterine Carcinoma.** (Eng) Anonymous (No affiliation given). *S Afr Med J* 52(28): 1105-1106; 1977.

Neither British nor American epidemiologic studies have confirmed the hypothetical relationship between estrogen therapy and endometrial carcinoma. The relationship between oral contraceptives and endometrial or cervical cancer is also problematic. (18 refs.)

- 78-0621 **Dietary Factors in Hormone-dependent Cancers.** (Eng) Carroll, K. K. (Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada). *Curr Concepts Nutr* 6: 25-40; 1977.

An investigation was made of the influence of diet on hormone-dependent cancers, particularly breast cancer, since most of the experimental evidence on this subject has com



om studies of mammary cancer. Animal studies indicate that restricting the caloric intake inhibits the development of mammary tumors and that increasing the fat level in the diet stimulates mammary tumor development. The effect of dietary fat appears to be largely independent of caloric intake, and the high fat diet is effective only when it is given after animals have been exposed to a carcinogen. This suggests that dietary fat acts as a promoting agent. Unsaturated fats seem to be more effective than saturated fats in promoting mammary tumorigenesis; it is not certain whether this difference is related to their content of essential fatty acids. Epidemiological data on human populations show a strong positive relation between dietary fat intake and breast cancer mortality. Breast cancer mortality is also positively correlated with total caloric intake and with intakes of animal protein and simple sugars, but not with intakes of vegetable proteins or complex carbohydrates. Positive correlations have also been observed between fat intake and certain other types of cancer, including prostatic and ovarian cancer. (58 refs.)

0622 **Dietary Fiber and Cancer.** (Eng) Kritchevsky, D. (Wistar Inst. Anatomy and Biology, Philadelphia, PA); Story, J. A. *Curr Concepts Nutr* 6: 41-54; 1977.

studies of the role of dietary fiber in colon carcinogenesis are reviewed. Epidemiological studies have indicated that one of the most common among large bowel diseases is a diet low in fiber. Other studies have found a high positive correlation between the incidence of breast and colon cancer and total fat and animal protein, but practically none with dietary fiber. These observations are explained by the fact that populations that ingest a diet high in animal products generally eat less fiber. There is evidence to support the theory that bile acids may be converted to carcinogenic hydrocarbons by bacterial action. In one study, a straight-line relationship was obtained when total fecal dihydroxycholeanoic acids were related against the incidence of colon cancer in six different populations. The hypothesis that bile acids are potential precursors of carcinogens and that the required metabolic changes can be brought about by intestinal bacteria has led to an intense study of the role of dietary fat, dietary animal products, and lack of dietary fiber in the genesis of colon cancer, but no conclusive results have been obtained. (24 refs.)

0623 **Modern Concepts in Nutritional Status and Foreign Compound Toxicity.** (Eng) Campbell, T. C. (Dept. of Nutritional Sciences, Cornell Univ., Ithaca, NY). In: *Modern Concepts in Safety Evaluation*. Mehlman, M. A.; Shapiro, I.; Blumenthal, H., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology, Vol. 1, Part 1, 544 pp; 11-1976.

influence of nutritional status on toxicity is reviewed, and protocols for experimental work are suggested. Dietary fiber

content has been associated with cancer of the colon, diverticulitis, and appendicitis. Current studies are attempting to establish an inverse relationship between dietary fiber and colon carcinoma. Cycasin induces cancer of the colon in normal but not germfree rats, presumably because of the lack of activation by bacterial flora. A similar mechanism could explain the ability of riboflavin to modify the carcinogenicity of certain azo dyes. Vitamin A deficiency permits development of colon carcinoma in rats exposed to aflatoxin B<sub>1</sub>, but it has no effect on hepatocarcinogenesis. Furthermore, during acute aflatoxicosis, hepatic and serum levels of vitamin A are depressed. It is suggested that a vitamin A deficiency predisposes cells to neoplastic change. A moderate protein deficiency can enhance the cellular immune response as a result of a lack of blocking serum antibody; this phenomenon can be correlated with a marked inhibition of tumor growth. The endocrine and cell-mediated immune systems may work as intervenors in the dietary modification of chemical tumorigenesis. The roles of macro- and micronutrient deficiencies in the functioning of the microsomal mixed-function-oxidase system are outlined. (131 refs.)

78-0624 **Diet, Nutrition, and Cancer.** (Eng) Petering, H. G. (Dept. Environmental Health, Univ. Cincinnati Medical Center, Kettering Lab., Cincinnati, OH). *Adv Exp Med Biol* 91: 207-228; 1977.

The role of diet and nutrition in modifying tumor induction by chemical carcinogens in foods and feeds is reviewed. The food contaminants of major concern include mycotoxins, cycasin, nitrosamines, tannins, estrogens, pesticides, metals, polycyclic aromatic hydrocarbons, and cocarcinogens such as sterculic acid and malvalic acid. Protection against these carcinogens is provided by caloric restriction, dietary fiber, and specific nutrients or dietary constituents that enhance microsomal mixed function oxidase enzymes and immune responses. The latter include fatty acids, water-soluble vitamins, fat-soluble vitamins, proteins, zinc, and lead. (76 refs.)

78-0625 **The Arsenic Problems.** (Eng) Frost, D. V. (Nutrition Biochemistry, 17 Rosa Road, Schenectady, NY, 12308). *Adv Exp Med Biol* 91: 259-279; 1977.

Human health and biological data on arsenic are reviewed. Studies have yet to prove that exposure to arsenicals causes cancer; in fact, exposure to some appears to diminish risk: lung and other cancer rates have been reported to be related inversely to dietary As intake. Other biological roles of AS, and its potential value as a dietary supplement are also discussed. (83 refs)

78-0626 **Inhibitors of Chemical Carcinogenesis.** (Eng) Wattenberg, L. W. (Dept. Lab. Medicine, Univ.



Medicine, Minneapolis, MN). *Adv Cancer Res* 26: 197-226; 1978.

Various inhibitors of chemical carcinogens are reviewed with emphasis on antioxidants and modifiers of the mixed function oxidase system. The former exert an inhibitory effect when administered 2 to 4 hr before the carcinogen. These inhibitors include butylated hydroxyanisole, butylated hydroxytoluene, ethoxyquin, disulfiram, benzyl isothiocyanate, selenium salts, and cysteamine HCl. Compounds modifying the mixed function oxidase system have a max effectiveness when administered 24-48 hr prior to challenge by the carcinogen. Compounds that increase enzyme activity include  $\alpha$ -benzene hexachloride, phenobarbital,  $\beta$ -naphthoflavone, and phenothiazine; a compound that acts by inhibiting the system is  $\alpha$ -naphthoflavone. In general, inhibitors alter the metabolism of the carcinogen, scavenging the active molecular species of the carcinogen to prevent interaction with the target sites. Many inhibitors are specific for certain carcinogens and only work within a certain dose range. Because of the lack of similarity among these inhibitors, many more may exist. Before inhibitors can be administered to the general population, experiments must reveal minimal toxicity and/or no harm must be demonstrated from accidental exposure incidences. Under no circumstances should inhibitors be administered to persons so that their exposure to carcinogens can be increased. (92 refs)

**78-0627 The Inhibitory Effect of Copper on Ethionine Carcinogenesis.** (Eng) Brada, Z. (Papanicolaou Cancer Res. Inst. at Miami, Univ. Miami, Miami, FL, 33123); Altman, N. H. *Adv Exp Med Biol* 91: 193-206; 1977.

Studies of the inhibitory effect of cupric acetate (CuAc) on the induction of hepatocellular carcinoma by DL-ethionine (E) and of the role of S-adenosylethionine (AE) in E carcinogenesis are reviewed. Although 100% of rats fed 0.3% or 0.6% E for 9 mo developed tumors, rats fed E plus the same amount of CuAc remained tumor-free. Short exposures to E alone increased the excretion of free E and AE at the expense of total ethionine sulfate (ES). With extended feeding, total ES excretion normalized, but free E and AE excretion decreased. In rats fed E + CuAc, ES excretion decreased and that of AE increased throughout the 56-day feeding period. Liver AE concentrations increased after the addition of CuAc to the diet, partly as a result of the diminished capacity of the rats to acetylate ES. Liver concentrations of ES and free E increased concomitantly, with the latter increase being a function of E intake and not the result of reduction of ES to E. (23 refs.)

**78-0628 Role of Interaction of Environmental Agents in Modifying Their Biological Activity.** (Eng) Nelson, N. (Inst. Environmental Medicine, New York Univ.

Medical Center, New York, NY). In: *Concepts in Safety Evaluation*. Mehlman, M. A.; Shapiro, R. E.; Blumenthal, H., eds. (New York: John Wiley & Sons): Advances in Modern Toxicology. Vol. 1, Part 1, 455 pp; 3-9; 1976.

Carcinogenesis probably results from the interaction of two or more environmental agents, whose effectiveness in producing cancer depends on host susceptibility. Irritating or nonirritating physical agents may stimulate a harmless substance or potential carcinogen to an active one. Furthermore, a mutation may remain dormant for years before it is stimulated to proliferate. (28 refs.)

**78-0629 Carcinogenesis Studies in Human Cells and Tissues.** (Eng) Harris, C. C. (Experimental Pathology Branch, Carcinogenesis Res. Program, NCI, Bethesda, MD, 20014); Saffiotti, U.; Trump, B. F. *Cancer Res* 38(2): 474-475; 1978.

The development of techniques for studying chemical carcinogenesis in human tissues and cells is reviewed. The major topics covered are (1) isolation and monolayer culture of human epithelial cells, (2) explant culture of human tissues, (3) xenotransplantation, (4) metabolism of chemical carcinogens, and (5) mutagenesis and neoplastic transformation of human cells. (no refs.)

**78-0630 Response to 'Use of Statistics When Examining Lifetime Studies in Rodents to Detect Carcinogenicity'.** (Eng) Haseman, J. K. (Biometry Branch, Nat. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709). *J Toxicol Environ Health* 3(4): 633-636; 1977.

The criticism that hypothesis testing in carcinogenesis screening programs is an inappropriate use of statistics is refuted. Despite problems associated with the tests, their careful use by a competent statistician can aid the toxicologist in interpreting the results of long-term carcinogenicity studies. (4 refs.)

**78-0631 Response to 'Use of Statistics When Examining Lifetime Studies in Rodents to Detect Carcinogenicity'.** (Eng) Fears, T. R. (Office of Field Studies and Statistics, NCI, Bethesda, MD 20014); Tarone, R. E. *J Toxicol Environ Health* 3(4): 629-632; 1977.

It is emphasized in this report that the statistical analysis of animal experiments in the WCI Carcinogenesis Bioassay Program is not based on the "standard formulation of test of hypothesis". Thus, there is no excess of false negatives or false positives in test results. (4 refs.)



78-0632 **Concepts in Health Evaluation of Commercial and Industrial Chemicals.** (Eng) McNamara, B. (Toxicology Branch, Chemical Lab., Dept. Army, Aberdeen Proving Ground, MD). In: *New Concepts in Safety Evaluation*. Mehlman, M. A.; Shapiro, R. E.; Blumenthal, eds. (New York: John Wiley & Sons): Advances in Modern Toxicology. Vol. 1, Part 1, 455 pp; 61-140; 1976.

Guidelines governing the testing of chemicals destined for human exposure and the toxicity tests used are presented. In the absence of detailed data, the lack of toxic signs should be used as a basis for evaluating the safety of a chemical. Satisfactory long-term no-effect doses can usually be determined within limits. However, the no-effect approach may not be suitable for new drugs. Chemicals of special economic or other interest should be tested extensively. (299 refs.)

78-0633 **Industry Group Offers Carcinogens Policy.** (Eng) Anonymous (No affiliation given). *Chem Eng News* 56(4): 6; 1978.

Proposals submitted by the American Industrial Health Council for regulating potential carcinogens in the workplace are listed. They include: development of dose-response data to establish a no-dose effect level; regulation according to toxicity; use of human epidemiological data for establishment of risk; use of in vitro tests only for screening and not as a basis for regulation; and use of personal protective equipment to lower exposure rather than engineering controls. (no refs.)

78-0634 **The Proper Perspective--Industry's View.** (Eng) American Industrial Health Council (No affiliation given). *Chem Eng News* 56(5): 30-35; 1978.

The Occupational Safety and Health Administration's (OSHA) proposal that most cancers are related to industrial exposure is rebutted. It is suggested that only 1%-5% of all cancers are related to industrial chemical exposure. OSHA should take a more realistic viewpoint on limiting exposure and it should expedite individual rules for chemicals with known or suspected carcinogenic hazard. (no refs)

78-0635 **Cancer Following Occupational Exposure to Asbestos and Vinyl Chloride.** (Eng) Nicholson, J. (Dept. Community Medicine, Mt. Sinai Sch. Medicine, New York, NY 10029). *Cancer [Suppl]* 39(4): 1792-1801; 1977.

A review is presented of occupational cancer caused by exposure to asbestos and vinyl chloride (VC). The population at risk for several asbestos-related cancers includes those han-

dling the mineral directly, those working near the application or removal of asbestos materials, and those living near an asbestos operation or in the household of an asbestos worker. Asbestos exposure has been connected with death from lung cancer, gastrointestinal cancer, and mesothelioma. The interval from first exposure to cancer development is at least 20 yr. A synergistic effect has been demonstrated for lung cancer in asbestos workers who smoke cigarettes. Exposure to VC has caused hemangiosarcoma of the liver in addition to excess mortality from tumors of the brain, lung, and lymphatic and hematopoietic systems. Exposures in the polyvinyl chloride processing industry have been reduced significantly by alteration of production methods to minimize residual VC monomer in the resin. Attempts to control asbestos exposures have not been as successful, partly as a result of significant differences between the two industries. A new standard for occupational asbestos exposure of 9.1 f/cm<sup>3</sup> has been proposed, which if adopted and enforced will greatly lower the human risk from asbestos exposure. (39 refs.)

78-0636 **Asbestos Carcinogenesis.** (Eng) Langer, A. M. (Environmental Sciences Lab., Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029); Wolff, M. S. *Adv Exp Med Biol* 91: 29-55; 1977.

The association between asbestos exposure and risk of asbestosis and cancer of the pleural and peritoneal mesothelium, lung, and gastrointestinal tract is reviewed. Factors to be considered in asbestos carcinogenesis include fiber type, duration of exposure, cofactors such as smoking, particle size and shape, and absorbed hydrocarbons and metals on the fibers. A model of asbestos activity using chrysotile asbestos is presented. More work on silicate carcinogenesis in animals is necessary to obtain additional information on the in vivo interaction. (162 refs)

78-0637 **Beryllium Carcinogenesis.** (Eng) Reeves, A. L. (Sch. Medicine, Wayne St. Univ., Detroit, MI). *Adv Exp Med Biol* 91: 13-27; 1977.

Experimental and epidemiological data on beryllium carcinogenesis are reviewed. Rabbits develop osteosarcoma after inhalation or iv administration of Be, and rats develop pulmonary carcinoma following inhalation or intratracheal injection of Be. The median effective total dose is approx 10 mg iv (expressed as zinc beryllium silicate) in the rabbit and approx 20  $\alpha$ /meter<sup>3</sup> (expressed as atmospheric beryllium sulfate concentration) in rats according to inhalation exposure studies lasting 3 mo. In other studies, bone sarcomas have occurred in mice and pulmonary adenocarcinomas in monkeys following Be exposure. Guinea pigs, hamsters, chickens, dogs, cats, and goats have no known neoplastic response to Be. Human epidemiological studies suggest an association



between Be exposure and lung cancer, but the data are not conclusive. The immune response governs the susceptibility or resistance of guinea pigs to berylliosis, and similar responses appear to work in man. The carcinogenic response may involve interference with nucleic acid function at the transcriptional level. (50 refs)

- 78-0638 Ionizing Irradiation and the Induction of Clinically Significant Disease in the Human Thyroid Gland.** (Eng) Maxon, H. R. (Radioisotope Lab., Cincinnati General Hosp., Cincinnati, OH 45267); Thomas S. R.; Saenger, E. L.; Buncher, C. R.; Kereiakes, J. G. *Am J Med* 63(6): 967-978; 1977.

Risk estimates were developed for acute thyroiditis, hypothyroidism, and benign and malignant thyroid nodules following exposure of the human thyroid to external and internal sources of ionizing radiation. Information from human exposure to  $^{131}\text{I}$  and to external radiation was used, and data from several different populations subjected to radiation under various circumstances were combined. The estimates include, whenever possible, corrections for the spontaneous occurrence of thyroid disease in human populations not subjected to radiation. Children and adults appear to be equally susceptible to the induction of cancer by  $^{131}\text{I}$  and by external irradiation. At external radiation doses < 2,000 roentgen-equivalent-man (rem), a linear no-threshold model suggests an absolute risk of 4.2 cases/million persons/rem/year for thyroid cancer. There appears to be a gradual decrease in risk at doses of 2,000-3,000 rem. External radiation at doses > 2,000-3,000 rem and  $^{131}\text{I}$  at doses > 60,000 rem appear to cause thyroid ablation with no subsequent risk of thyroid neoplasm in children and adults. Limited data suggest that the absolute risk for cancer induction in children exposed to  $^{131}\text{I}$  is 0.06 case/million persons/rem/year. The dose-response relationship may not be linear in this situation. Until this issue can be clarified further, it should be assumed that, based on radiation dosimetry,  $^{131}\text{I}$  is one-twentieth as effective as external radiation therapy in the induction of thyroid nodules. (59 refs.)

- 78-0639 The Genetic and Somatic Effects of Radiation: A Balance Between Benefits and Risks.** (Eng) Merz, T. (Box 87, Medical Coll. Virginia, Richmond, VA 23298). *Med Coll VA Q* 13(4): 157-159; 1977.

The effects of low doses of ionizing radiation are listed for germ and somatic cells. Although somatic cell damage can lead to leukemia, radiation exposures associated with typical diagnostic procedures are usually under the permissible dose of 0.5 rads/yr. If the normal incidence of a disease is 1/100,000 persons, doubling the risk as a consequence of radiation exposure increases it only to 2/100,000. (5 refs.)

- 78-0640 II. Epidemiology Studies of Irradiated Populations.** (Eng.) Miller, R. W. (Epidemiology Branch, NCI, Bethesda, MD 20014). *RI Med J* 60(1): 475-481; 1977.

The effects of radiation in various populations are reviewed. The association between whole- or partial-body exposure and leukemia is well-known, and cases from Japan and the British Isles are cited as representative examples. Studies have also indicated that preception, intrauterine, maternal, or paternal radiation exposure results in approx a 50% increase in leukemia and other tumors in offspring. Thyroid cancer has been shown to result from head, neck, and thymus irradiation for various causes. Radioisotopes have also been shown to cause thyroid cancer, even in utero, and the Bikini atoll studies are cited as examples. Thorotrast has been shown to cause liver cancer, leukemia, and bone cancer. In one study  $^{224}\text{Ra}$  given as therapy for tuberculosis of bone caused bone tumors in 36/224 children and benign bone tumors in 2 more are expected. Some diseases that increase susceptibility to cancer are xeroderma pigmentosum, ataxia telangiectasia, Down's syndrome, Bloom's syndrome, and Fanconi syndrome. The involvement of radiation in congenital malformations and genetic alterations is also reviewed (no refs.)

- 78-0641 Virological Aspects of Head and Neck Cancer.** (Eng) Costa, J. C. (Viral Oncology and Molecular Pathology Section, Lab. Pathology, NCI, Bethesda, MD 20014). In: *Head and Neck Cancer. State of the Art Conference. February 16, 17 and 18, 1976.* (St. Louis, MO: Laryngoscope: Vol. 88, No. 1, Part 2, Suppl. 8, pp. 57-58; 1978.

The possible association between adenoviruses, herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV) or papilloma virus and human head and neck cancers is reviewed. Although adenoviruses are etiologic agents of upper respiratory diseases in man, there is no evidence of adenovirus genetic information in human tumor cells. Epidermoid carcinoma occasionally arises at the site of recurrent herpes infection and antibodies to a nonstructural antigen of HSV-1 were elevated in at least one study of patients with squamous cell carcinoma of the head and neck. It is not known if the HSV genome or antigens are present in human squamous cell tumors of the head and neck. EBV may play an etiological role in nasopharyngeal carcinoma. Minor differences among EBV's associated with mononucleosis, Burkitt's lymphoma and nasopharyngeal carcinoma could explain the wide range of biological properties of EBV. There is an association between laryngeal papillomas in children and the presence of condyloma acuminata (caused by papilloma virus) in the birth canal of the mother at the time of delivery. Extracts of laryngeal papillomas have been shown to produce warts when injected into the skin of volunteers. (no refs.)



**78-0642 Latent Characteristics of Selected Herpesviruses.** (Eng) Stevens, J. G. (Dept. Microbiology and Immunology, Sch. Medicine, Univ. California, Los Angeles, CA). *Adv Cancer Res* 26: 227-256; 1978.

This review of selected herpesviruses, current evidence suggests a strong association between the nervous system and infection by herpes simplex virus types I and II and *Herpesvirus simiae*; between lymphoid tissue and Epstein-Barr virus (EBV), Marek's disease virus, *H. ateles*, *H. saimiri*, and *H. ilagius*; and between epithelial tissue and the Lucke agent EBV. Special attention is focused on herpes simplex virus, EBV, and Lucke virus. EBV is maintained in a latent state in the neoplastic B lymphocytes of Burkitt's lymphoma and in some epithelial cells of nasopharyngeal carcinoma; it may be an etiological agent in these cancers. (120 refs)

**78-0643 Herpesviruses and Cancer.** (Fre) Rickinson, A. B. (l'Universite de Bristol Grande, Brittany, France). *Recherche* 8(84): 1049-1057; 1977.

Herpesviruses are known to infect man: herpes simplex virus types 1 and 2, varicella virus, cytomegalovirus, and Epstein-Barr virus. Herpes simplex type 2 has been implicated in cancer of the cervix, and Epstein-Barr virus has been implicated in Burkitt's lymphoma and nasopharyngeal carcinoma. The role of herpesviruses in animal malignancies is reviewed. (4 refs.)

**78-0644 Cassandra Still a Myth (Letter to Editor).** (Eng) Kaufman, R. H. (Baylor Coll. Medicine, Houston, TX); Bertner, E. W.; Friedrich, E. G. *JAMA* 238(22): 3183; 1977.

Although herpes simplex viral infections have been associated with carcinomas of the vulva and penis in untreated patients and are implicated in carcinoma of the cervix, there is no evidence that photoinactivated herpes virus induces tumors in adult humans. A recent report should have indicated that the virus may cause severe atypias, but that this may vary in the presence or absence of photodynamic dye therapy. (3 refs.)

**78-0645 The Genetic Structure of RNA Tumor Viruses.** (Eng) Vogt, P. K. (Dept. Microbiology, Univ. Southern California, Sch. Medicine, Los Angeles, CA 90033); S. S. *Annu Rev Genet* 2(11): 203-238; 1977.

The genetic structure of RNA C-type oncoviruses is reviewed, and the physiology of these viruses is discussed in

reference to known mutants. Following a discussion of the physical properties of the viral genome, the four viral genes (*gag*, *pol*, *env*, and *src*) are identified. The first three are essential for virus replication, and the *src* gene is required exclusively for sarcomagenic transformation. Viral genes for carcinoma or leukemic transformation have not been identified. Recombination, gene mapping, and viral RNA synthesis are also considered. Little is known about the interaction between the viral and host genome in both reproduction and oncogenic transformation. Detection of a transforming protein and design of a biological assay for it are important goals in the study of these viruses. (374 refs.)

**78-0646 Retroviruses and Cancer.** (Eng) Baltimore, D. (Dept. Microbiology, Massachusetts Inst. Technology, Cambridge, MA). *Hosp Pract* 13(1): 45-47; 1978.

The initial step in the replication of oncogenic retroviruses is the reverse transcription of their RNA into DNA. Replication is reviewed with emphasis on the incorporation of viral DNA into a host's cell chromosome and the virus-directed synthesis of a transforming protein. The possibility that retroviruses can permanently alter a cell's genetic material is also discussed. (7 refs.)

**78-0647 RNA-dependent DNA Polymerase (Reverse Transcriptase).** (Eng) Bauer, G. (Max-Planck-Institut für Biochemie, Abteilung Virusforschung, D-8033 Martinsried bei München, W. Germany). *Blut* 35(1): 3-9; 1977.

Evidence is reviewed that suggests that reverse transcriptase (RT) might be part of the normal enzyme set of certain premature cells found only in the bone marrow of healthy people, whereas in leukemia patients, the cells are found in the peripheral blood. A review of RT activity in animal model systems indicated that normal embryonic chicken cells synthesize the enzyme, cells producing endogenous virus possess viral RT activity but are not transformed, and that cells infected by exogenous RNA tumor viruses possess viral RT activity and may or may not be transformed. (30 refs.)

**78-0648 Interaction Between Viral and Genetic Factors in Murine Mammary Cancer.** (Eng) Hilgers, J. (Netherlands Cancer Inst., Amsterdam, Netherlands); Bentvelzen, P. *Adv Cancer Res* 26: 143-195; 1978.

The association between genetic susceptibility to murine mammary tumorigenesis and exogenous virus infections and the association between genetic control of release of endoge-



nous viruses and subsequent tumorigenesis are reviewed. Special attention is focused on the transmission of mammary tumor virus by transplacental, extrachromosomal, or horizontal means; the genetics of susceptibility to exogenous mammary tumor virus; the role of the C3Hf and GR systems in endogenous virus expression and mammary tumor development, and molecular biology studies indicating the role of viruses in mouse mammary tumor development. (259 refs)

- 78-0649 Interactions Between Host and Viral Genomes in Mouse Leukemia.** (Eng) Steeves, R. (Dept. Developmental Biology and Cancer, Albert Einstein Coll. Medicine, Bronx, NY 10461); Lilly, F. *Annu Rev Genet* 2(11): 277-296; 1977.

The effects of chromosomally integrated murine leukemia virus (MuLV) genomes, host genes that affect response to MuLV by influencing cellular differentiation, genes that alter various stages of MuLV growth, genes that control the outgrowth of tumor cells, and viral genes that affect the tropism or pathogenicity of the virus, are reviewed. Although transformation in lymphatic leukemia is not completely understood, pretransformational events include the occurrence of appropriate target cells, the occurrence of the MuLV genome, the presence of cell-surface receptors for attachment and penetration of the infectious virions, and viral replication within the cells. Following transformation, extensive cellular replication must occur to produce a clinically recognizable disease. A provocative case can be made for the hypothesis that all leukemias in mice are in some way associated with C-type viruses. Environmental agents such as x-rays and chemicals may be important factors. However, until it is known how chemical and physical environmental agents interact with the host and viral genomes, leukemogenesis in mice will not be understood completely. (129 refs.)

- 78-0650 Immunogenetics of Cell Surface Antigens of Mouse Leukemia.** (Eng) Old, L. J. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Stockett, E. *Annu Rev Genet* 2(11): 127-160; 1977.

The various categories of cell-surface antigens that are identified with murine leukemia are reviewed, with emphasis on those antigens defined serologically. Specific topics include techniques for the in vitro analysis of surface antigens of leukemia cells, cell-surface antigens related to naturally occurring murine leukemia viruses, cell-surface antigens of the thymus leukemia system, and mammary-leukemia surface antigen of murine leukemia. None of the murine leukemia virus-related surface antigens can be considered transformation-specific, because they are also found on nonmalignant virus-infected cells. Various possible sources of tumor-specific antigens are proposed. (97 refs.)

- 78-0651 Immune Surveillance System: Its Failure and Activation.** (Eng) Shearer, W. T. (Dept. Pediatrics, Washington Univ. Sch. Medicine, St. Louis, MO); Fink, M. P. *Prog Hematol* 10: 247-310; 1977.

A review of evidence for the existence and function of an immunosurveillance system that protects against the growth and development of malignant tissues is presented. The various mechanisms of cytotoxicity exerted by the immune system are presented. Stimulation of the immune system to augment the body's response to a tumor growth holds promise for future treatment. (466 refs)

- 78-0652 Recognition and Destruction of Target Cells by Tumoricidal Macrophages.** (Eng) Fidler, I. J. (Basic Res. Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701). *Isr J Med Sci* 14(1): 177-191; 1978.

When rendered tumoricidal in vitro by incubation with mediators released by rat lymphocytes in response to an antigen or a mitogen, mouse macrophages discriminated between neoplastic and normal cells. Tumoricidal mouse macrophages recognized and destroyed in vitro syngeneic allogeneic, and xenogeneic tumor cells but not normal cells even when tumor and normal cells were cocultivated with the tumoricidal macrophages. Target recognition and destruction were independent of tumor-associated transplantation antigens, histocompatibility antigens, lymphocyte-mediated cytotoxicity, rate of cell division, and expression of murine C type viruses. Tumoricidal mouse macrophages did not kill xenogeneic normal rat fibroblast cell line (3Y1) at either 33 or 40 C. Wild-type simian virus 40 (SV40)-transformed rat fibroblasts (SV68/3Y1) or those transformed with a temperature-sensitive A cistron mutant of SV40 (ts 640/3Y1) were killed at both 33 and 40 C. Since ts 640/3Y1 cells express SV40 T antigen at 33 but not at 40 C, these results suggest that macrophage killing occurred independently of SV40 T antigen expression. The susceptibility of target cells to destruction by macrophages correlated with their tumorigenicity in nude mice. Tumoricidal macrophages may be a suitable biological tool for the detection and identification of transformed, tumorigenic cells in vitro across species barriers. (5 refs.)

- 78-0653 Serum Factors Which Suppress the Immune Response.** (Eng) Tomasi, T. B. (Dept. Immunology, Mayo Medical Sch., Mayo Clinic, Rochester, MN 55901). In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 215-250, 1977.

The nonantigenic specific serum suppressor factors that have been sufficiently characterized to suggest that the



a role in normal immune regulation or in immune abnormalities seen in certain diseases are reviewed. Unoregulatory  $\alpha$ -globulin (IRA) appears to inhibit primarily T- and not B-cell-mediated reactions. Suppression of delayed hypersensitivity reactions and mitogen responsiveness have been shown in humans and experimental animals with malignant tumors. The serum suppressive factors in the tumor-bearing host have generally been found in the  $\alpha$ -globulin fractions, which are frequently elevated in advanced cancer. Inhibitory serum  $\alpha$ -globulin of amyloid (SAA) is present in small amounts in normal serum and is markedly elevated in secondary amyloidosis, cancer, and other chronic inflammatory diseases. Some evidence exists that  $\alpha$ -fetoprotein (AFP) may have immunoregulatory properties in animal models and in human diseases. Data on two carcinogen-induced tumors show that the spleens of tumor-bearing animals have elevated surface AFP and that these cells can synthesize AFP in vitro. The splenic synthesis of AFP in lymphomatous animals may result from a blastogenic reaction of the host against tumor-specific antigens and the AFP may be produced by the host lymphocytes and/or macrophages, rather than the tumor cells. In patients with malignant lymphomas, 8/10 lymph node or spleen samples infiltrated with lymphomatous cells showed AFP-bearing cells. Several cancer families have a high incidence of peripheral blood monocytes bearing surface AFP. None of the patients with positive cells showed significant elevations of serum AFP. It is speculated that AFP produced locally in sufficient concentration may be suppressive and thus influence the growth of malignant cells even in the absence of systemic immunorepression. (79 refs.)

**78-0654 Metabolic Immunodepression Which Increases the Risk of Cancer.** (Eng) Dilman, V. M. (Prof. V. M. Petrov Res. Inst. Oncology, Leningrad, USSR). *Lancet* 1977; 1:1207-1209; 1977.

Metabolic changes that result in increased blood levels of free fatty acids (FFA), insulin, cholesterol, or triglycerides are followed by a decrease in cellular immunity. These metabolic changes also promote the division of somatic, nonlymphoid cells, a combination of effects that encourages carcinogenesis. The activity of any function controlled by the hypothalamic feedback mechanism may be intensified if the hypothalamic threshold of sensitivity to homeostatic stimuli is raised. This occurs in aging and accounts for the fact that similar hormonal and metabolic patterns are observed in stress, normal aging, and pregnancy. Many chemical carcinogens raise the hypothalamic threshold to feedback control mechanisms, decrease insulin tolerance, and increase blood insulin, changes associated with cancer proneness. It is concluded that cancer proneness develops whenever there is a shift toward the dominant utilization of FFA. This occurs with pregnancy, rapid growth, stress, normal aging, obesity, adult-onset diabetes, and exposure to some chemical carcinogens. (56 refs.)

**78-0655 The Transmissible Venereal Tumor of the Dog—A Naturally Occurring Allograft? A Review.** (Eng) Cohen, D. (Unit Comparative Medicine, Faculty Health Sciences, Ben-Gurion Univ. Negev, Beersheba, Israel). *Isr J Med Sci* 14(1): 14-19; 1978.

Current knowledge concerning the transmissible venereal tumor of the dog (TVT) is presented. The tumor is transmitted by coitus or by experimental transplantation of living tumor cells. Injury to the vaginal or penile mucosa during intercourse probably facilitates the spread of this tumor. It has a worldwide distribution, and incidence appears to be related to the amount of control exercised over a dog population. Tumor cells are characterized by a stemline chromosomal number of 59, compared to the normal dog karyotype of 78. However, the total amount of DNA and the number of chromosomal arms in TVT cells are close to those in normal cells. Complete tumor regression is followed by transplantation immunity, and humoral antibodies to the tumor can be detected in TVT-bearing animals. Natural transplantation of cells is suggested to be the mode of transmission. BCG stimulation of tumor-bearing animals results in tumor regression within a shorter period of time than that in nonstimulated tumor-bearers and a significant increase in the mixed lymphocyte tumor culture response. (41 refs.)

**78-0656 Specific Immunotherapy for Adenocarcinoma with Anti-A and Anti-P<sub>1</sub> for Prevention of Metastasis.** (Eng) Levine, P. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 75-79; 1977.

The prevention of metastasis by antibodies is illustrated by the case of a 66-yr-old woman of genotype *pp* who, after subtotal gastrectomy for removal of an adenocarcinoma, survived metastasis-free for 22 yr. Her serum contained a complex of three antibodies identified as anti-P<sub>1</sub>P<sub>2</sub>Pk (titer 1:4-1:8), and her long survival may have been due to the very high titer (1:512) that resulted from the iv injection of 25 ml of incompatible blood in a test for compatibility. Evidence that this cytotoxicity was caused by IgG molecules, which are characterized by long duration in the absence of further antigenic stimulation, was obtained in studies of the significantly high incidence of spontaneous abortions in genotype *pp* women. The anti-P<sub>1</sub> of the anti-P<sub>1</sub>P<sub>2</sub>Pk in these women and the high-titered antibody in the adenocarcinoma patient exerted a similar highly specific cytotoxic effect on P<sub>1</sub> sites, whether they were the P<sub>1</sub> sites on the tissues of the early P<sub>1</sub> fetus or the illegitimate P<sub>1</sub> sites in the malignant tissue. In studies of breast adenocarcinoma, attempts are being made to increase the titer of anti-T by inoculating these patients with a vaccine consisting of antigen T extracted from normal RBC and the autologous adenocarcinomatous breast, plus a small amount



of BCG. The increased anti-T titer will hopefully prove cytotoxic to the T antigen in the malignancy and, hence, to the malignancy itself, thus preventing metastasis. Mastectomy also increases the anti-T titer, as the T antigen in the malignant tissue continually absorbs anti-T in vivo. (12 refs.)

**78-0657 Alpha-Chain Disease and Lymphoma of the Small Intestine: Memorandum.** (Fre) World Health Organization (Immunology Service, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland). *Bull Who* 55(5): 587-597; 1977.

In this review of the literature on Mediterranean lymphomas of the intestine (IPSID: immunoproliferative disease of the small intestine), information on the clinical, immunological, histopathological, epidemiological, and therapeutic aspects of the disease is updated. The highest incidence of IPSID is in North Africa and Southwest Asia; however, populations in India, South and Central America, South Africa, and Europe along the Mediterranean are also affected. Race or ethnic origin does not appear to play a role in incidence, but socioeconomic origin does, since disadvantaged populations are principally affected. IPSID is found equally among men and women, usually in the age group 20-40 yr. During the premalignant phase of the disease, there is a plasmacyte or mixed lymphocyte-plasmacyte infiltration of the small intestinal mucosa. In the malignant phase, circumscribed or diffuse sarcomas are found in the intestine, lymph nodes, and mesentery. A diagnostic feature of IPSID is the presence of an abnormal immunoglobulin population composed of incomplete alpha chains without light chains. Studies have not been made of the immunocompetence of patients with IPSID or of the level of intestinal immunoglobulins or presence of tumor antigens. Early treatment with antibiotics, principally tetracycline and ampicillin, results in total remission, which indicates an environmental etiology for the disease. (41 refs.)

**78-0658 The Genetics of Human Cancer.** (Eng) Croce, C. M. (Wistar Inst. Anatomy and Biology, Philadelphia, PA); Koprowski, H. *Sci Am* 238(2): 117-125; 1978.

Data on the role of human chromosomes in cancer are reviewed. Conditions such as retinoblastoma and polyposis can be inherited, but apparently a triggering mechanism is required for cancer, as not all cells genetically predisposed to this disease form tumors. Changes in chromosomal composition are associated with some tumors: translocation of the long arm of chromosome 22 to chromosome 9 is associated with chronic myelogenous leukemia, deletion of one end of chromosome 22 is associated with meningioma, and deletion of the long arm of chromosome 13 is associated with retinoblastoma. Hybrid experiments with human and mouse cells

have indicated that simian virus 40 can become incorporated into human chromosome 7 or 17 and that the resultant cells are tumorigenic. Loss of either chromosome from the hybrid abrogates the neoplasticity. The tumor-forming ability of RNA-containing viruses appears to be inherited as a dominant trait. An example of a tumor formed by a change in gene function and not by an addition or deletion from a chromosome is the teratoma. (4 refs)

**78-0659 Genetics and Cancer.** (Eng) Mueller, J. M. (Medical Oncology, Medical Coll. Virginia Commonwealth Univ., Richmond, VA 23298); Diasio, R. B. *Med Coll Va Q* 13(4): 154-156; 1977.

The genetics of human cancer can be divided into three categories: cancers inherited by direct gene transmission; familial disorders that predispose to cancer; and site-specific cancers with a possible familial occurrence. Examples of each category are presented. (14 refs.)

**78-0660 Cancer: The Eighth Plague--A Suggestion for Pathogenesis.** (Eng) Bluming, A. Z. (Hematology, Univ. Southern California Sch. Medicine, Los Angeles, CA 91436). *Isr J Med Sci* 14(1): 192-200; 1978.

According to current concepts of cancer, the aggressive malignant cell constitutes the disease and therapy is based on the idea that a mutagenic event produced a clone of cells that must be excised, poisoned, or irradiated for cure. It is suggested instead that cancer results from a defect in the regulatory mechanisms controlling cellular proliferation. Immunosuppression or inhibition of regulation coupled with stimulation of cellular proliferation can increase the susceptibility of animals to cancer. Hypothetical pathogenetic mechanisms for malignant lymphoma suggest that this disease could in some cases be a poorly regulated proliferation of normal stimulated cells. Benign and malignant would thus be opposite poles of the same disease. Since leukemia cells infused into a normal environment do not induce leukemia and normal cells infused into a leukemic environment may produce leukemic progeny, a similar environmental cause may exist for leukemia. (refs.)

**78-0661 On the Nature of Metastasis.** (Eng) Day, S. B. (Sloan-Kettering Inst. Cancer Res., New York, NY 10021). In: *Cancer Invasion and Metastasis: Biological Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stancovski, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 5 pp.; 1-11; 1977.

A review of the classic viewpoint of metastasis is followed



outline of areas of current research. The latter include (1) the reciprocating partnerships between cells and the host-within-a-host relationship of virus, cell, and organism; (2) the molecular (vs cellular) aspects of metastasis; ie, in cancer, part of the whole perspective may be a combination of host response and differences in the cells themselves; (3) the theory that metastasis in humans is a cascade or multistep process, with the end being generalized dissemination; and in doing so could be responsible for the production of metastases. A final section gives answers to and attendant discussion of the following three questions posed to 21 members of a conference on cancer invasion and metastasis: Is a metastasis a cancer cell? (2) If it is a cancer cell, why is it so? (3) If a metastasis is not a cancer cell, why not? (The responses were 12, yes; 5, no; 4, qualified no). (14 refs.)

**78-0662 Tumor Angiogenesis: Its Possible Role in Metastasis and Invasion.** (Eng.) Folkman, J. (Dept. Surgery, Children's Hosp. Medical Center, Harvard Medical Sch., Boston, MA 02115); Tyler, K. In: *Cancer Invasion and Metastasis: Biological Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 17 pp.; 95-103; 1977.

Malignant tumors do not make their own vessels, but induce them from the host, as demonstrated by tumor implantation in rabbit cornea. Adult normal tissues did not stimulate neovascularization. Embryonic tissues did connect with normal vessels, but only if the graft was placed in direct contact with the vessels. However, implants of neoplastic cells were able to induce vessel proliferation across distances of up to 3.0 mm. In studies of T241 sarcomas implanted in the thighs of C57Bl/6 mice, tumor cells were not identified in the venous effluent until day 5, when all tumors had gained small vascular sprouts. This implies that few or no cells leave the tumor until after the new sprouts have penetrated its periphery. Indirect evidence that vascularization is necessary for tumor cells to escape into the circulation comes from studies of human carcinomas of the cervix, stomach, colon, bladder, and skin. During the in situ phase, the tumor is small, rests above an intact basement membrane, and is avascular. Contrary to animals, in which this avascular stage is extremely brief, the stage may exist for years in humans. It is also commonly free of metastases, which usually appear only after the primary has become vascularized. A static implant may need to reintroduce new vessels similar to those of the primary for further growth to occur. Dormant metastases can also result, from a variety of mechanisms. These are briefly explored along with the speculation that the lack of neovascularization may facilitate or activate tumor invasiveness. (22 refs.)

**78-0663 Discussion Summary: Current Experimental Approaches to Metastasis Control.** (Eng.) Day, S. B. (Sloan-Kettering Inst. Cancer Res., New York, NY 10021). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G., eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 415-416; 1977.

The mechanisms by which cyclophosphamide, *Corynebacterium parvum*, and sulfated polysaccharides retard tumor metastases are explored. The possibility that anesthesia accelerates metastases is also discussed, as is the relationship between tumor body burden and the response to surgery and adjuvant chemotherapy. (no refs.)

**78-0664 Cancer of the Liver: Pathogenesis and Recent Aetiological Factors.** (Eng.) Anthony, P. P. (Bland-Sutton Inst., Middlesex Hosp. Medical Sch., London W1, England). *Trans R Soc Trop Med Hyg* 71(6): 466-470; 1977.

The pathogenesis of experimental, chemically induced liver tumors, precursor lesions of liver cancer in man, and etiologic factors in the increasing incidence in Western countries are discussed. In tropical countries, where patients tend to develop cirrhosis and liver cancer simultaneously, mycotoxins and hepatitis B virus are the predominant etiologic factors. In Western countries, where cirrhosis often precedes hepatic neoplasms,  $\alpha$ -1-antitrypsin deficiency, alcoholism, plant carcinogens, nitrosamines, vinyl chloride monomer, anabolic/androgenic steroids, and oral contraceptive steroids may increase the cancer risk. (35 refs.)

**78-0665 Lactation and Mammary Carcinoma.** (Eng.) Alexander, G. A. (Howard Univ. Coll. Medicine, Washington, DC 20001). *Black Bag* 5(2): 73-76; 1977.

A review of the literature on breast feeding and mammary carcinoma reveals that the former confers no real protective effect against the latter. Pregnancy at a young age, however, is associated with a decreased risk. The different susceptibilities of women in different parts of the world may be due to endocrine factors, genetic factors, and viral infections. (38 refs.)

**78-0666 Editorial Comment.** (Eng.) Wilson, E. (No affiliation given); Greene, J. W. *Obstet Gynecol* 51(1): 105-106; 1978.

The origin of the pathophysiologic defect in polycystic ovarian disease and ovarian hyperthecosis is still uncertain. Refined hormone identification and quantitation techniques have led to new areas of investigation and several hypotheses on the origin of the defect. (19 refs.)



- 78-0667 **Malignant Melanoma--Reviewed.** (Eng) O'Connor, T. P. (Frenchay Hosp., Bristol, England). *Ir Med J* 70(15): 450-454; 1977.

The incidence, etiology, presentation, and treatment of malignant melanoma are discussed. The incidence is increasing, and it ranges from 3.9/100,000 population in southwestern England to 16/100,000 in Queensland, Australia. In addition to ultraviolet light, the etiologic factors may include a solar factor circulating in plasma and atmospheric pollution by jet exhaust and aerosol sprays. (14 refs.)

- 78-0668 **Neoplastic Transformation of Cells in the Gastrointestinal Tract of Man and Rodent.** (Eng) Lipkin, M. (Memorial Sloan-Kettering Cancer Center, New York, NY). In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 413-428; 1977.

The neoplastic transformation of gastrointestinal tract cells in humans and rodents is discussed based on data from the literature. In humans, atrophic gastritis and intestinal metaplasia are accompanied by increased thymidine labeling and mitotic indices in the gastric mucosa. Epithelial cells fail to repress DNA synthesis during migration through the gastric pits and undergo maturation. Microautoradiographic patterns of DNA, RNA, and protein synthesis become abnormal with increased pathology. In humans with adenomatosis of the colon and rectum (ACR; familial polyposis), progressive stages of abnormal growth also occur in colonic epithelial cells, as they develop an increased ability to proliferate and accumulate in the mucosa. A screening process has been developed based on changes in the human gastrointestinal tract that accompany neoplasia. Compared to control observations, a high frequency of labeling of surface epithelial cells and cytologic abnormalities are found in flat mucosa of inherited ACR. These findings are being quantitated, and a profile of human population groups at risk for colon cancer is being constructed. Recent evidence suggests that cutaneous fibroblasts of ACR patients have many characteristics of transformed cells. (59 refs.)

- 78-0669 **Precancerous Lesions of the Gastrointestinal Tract.** (Ger) Hermanek, P. (Abteilung für Klinische Pathologie, Chirurgische Universitäts-Klinik, Maximiliansplatz, 8520 Erlangen, W. Germany). *Fortschr Med* 96(3): 108-110; 1978.

Differentiation of the most prominent precancerous lesions of the gastrointestinal tract, including multiple polyps, polyposis, adenomatosis of the colon, and nonneoplastic polyposis is discussed. Without prophylactic colectomy cancer evolution is observed in 80% of the adenomatosis patients. Adenomatosis of the colon is too frequently diagnosed

since there is often a collection of numerous adenomas and an adenomatosis. Therapy for adenomatosis includes colectomy with ileorectostomy; nevertheless, 4% of the treated patients develop rectal carcinomas 10 yr posttreatment. Carcinoma evolution develops from the polyp-cancer sequence: the initial adenoma develops severe cell atypias, which lead to an adenoma with invasive carcinoma, and, finally, to polypous carcinoma. Patients with a long history of extensive or total ulcerative colitis have an increased risk for developing carcinomas. Precancerous dysplasias, originating from chronic ulcerative proctocolitis, develop over a period of 10 yr and require total colonic involvement. These dysplasias are observed in rectoscopic and/or colonoscopic biopsies. Borderline lesions of the stomach and true adenomas are considered precursors of gastric carcinomas. (12 refs.)

- 78-0670 **Plant Tumors due to Genetic Changes? Economic Benefits and Hazards of Plasmid Research.** (Ger) Beiderbeck, R. (Botanisches Institut, Universität Heidelberg, Hofmeisterweg 4, 6900 Heidelberg, W. Germany). *Bopp, M. Umschau Wiss Technik* 77(21): 698-703; 1977.

Recent research on plant tumor induction by *Agrobacterium tumefaciens*, which caused malignant growth (crown gall) in 634/1,176 plant species tested, is reviewed. The bacterium does not penetrate into the host cell, but the presence of live bacteria in plant wounds for only 48 hr is sufficient for tumor induction. Further tumors can be induced when tumor cells are grafted to other plants. It is not possible to induce tumors by the DNA and RNA isolated from *A. tumefaciens*. Tumor induction is inhibited by rifampicin and  $\alpha$ -amanitine in the early stage of the infection;  $\alpha$ -amanitine also inhibits RNA synthesis in plant cells. These findings indicate that RNA synthesis in both bacterium and plant cell is necessary for tumor induction. Short extrachromosomal fragments of *A. tumefaciens* DNA were isolated from tumor DNA. The virulence (tumor-inducing capacity) of *A. tumefaciens* is related to the presence of plasmid in the bacterium. Specific strains of *A. tumefaciens* induce tumors containing octopin or nopalins, and the corresponding strains are also able to metabolize these substances in the tumors. Consequently, the information for the metabolic properties of the tumors is carried by the bacterium plasmid. Subsequent graftings to normal plants may result in a reversion of the tumor to normal growth. The tumor-inducing plasmid of *A. tumefaciens* shows certain analogies to oncogenic viruses. There are no indications of the oncogenic effect of *A. tumefaciens* in animals and man. (4 refs.)

- 78-0671 **Genetic Markers and Cancer Epidemiology.** (Eng) Petrakis, N. L. (Hooper Foundation, Univ. California, San Francisco, CA 94143); King, M. C. *Cancer [Suppl]* 39(4): 1861-1866; 1977.

The use of genetic markers in investigating the etiology of



man cancers is considered. These investigations are subject to the serious problems of statistical significance and choice of appropriate control populations. Reported associations of particular genotypes with increased cancer susceptibility may be considered preliminary indications of possible significance. The investigation of genetic markers (such as the histocompatibility complex) that code for proteins of potential immunological or physiological importance in susceptibility or resistance to cancer offers promise of progress in cancer etiology. Studies of the genetic marker in women suggest that both genetic and environmental factors may interact to determine breast cancer risk among Oriental women. The lower cancer risk in Oriental women may be related to an overall decrease in the secretory activity of the nonlactating breast, which is especially marked in women with dry cerumen. A low level of secretory activity may minimize exposure of the breast epithelium to exogenous and endogenous carcinogens. Another approach involves linkage analysis, the statistical analysis of genetic markers in families with high cancer incidence. The application of linkage analysis to cancer would make it possible to determine which cancers have an important genetic component, to analyze the effect of loci whose protein products are not known but are closely linked to a genetic marker, and would make genetic counseling for affected families a real possibility. (41 refs.)

**78-0672 Gastrointestinal Carcinoma-Risk Groups.** (Ger) Rosch, W. (Medizinische Univ.-Klinik, Krankenhausstrasse 12, 8520 Erlangen, W. Germany). *Deutsche Zeitschrift für Medizin* 96(3): 102-107; 1978.

High-risk groups for gastrointestinal carcinoma include people with a familial predisposition and genetic defects, occupational exposure to hazardous substances (asbestos), previous surgery, long-standing bowel obstruction, and chronic inflammatory alteration of the mucosa. These groups account for about 5% of all gastrointestinal carcinomas. (32 refs.)

**78-0673 The Epidemiology of Large-Bowel Cancer.** (Eng) Correa, P. (Louisiana St. Univ. Medical Center, New Orleans, LA); Haenszel, W. *Adv Cancer Res* 26: 1-41; 1978.

Recent epidemiological data on large bowel cancer are reviewed. This cancer is characterized by large intercountry differences in risk, anatomic- and segment-specific patterns of risk, sex-specific patterns of risk, and a disease response modulated by events in adult life linked with migration to a new environment. In North America and Western Europe, large bowel cancer is linked to high-fat, high-protein diets and to the distribution of endocrine-dependent tumors and arteriosclerotic heart disease. The slopes of the age-specific incidence curves are consistently higher for men than women in all populations, and this is related to a male dominance in risk

after age 60-65. There also appears to be a strong association between adenomatous polyps and colon cancer. The main components of an etiological model are as follows: in low-risk areas, there is a preponderance of female cases and a relatively uniform distribution of cases throughout the length of the colon; when a new etiological factor is introduced, there is a rise in sigmoid cancer in older men followed later by a rise in women; when the cancer becomes epidemic, a rise in cecal and ascending colon cancer, is first noted in men, and is accompanied by similar shifts in the frequency of descending and transverse colon cancers. This model fits the hypothesis based on the presence, in the intestinal contents, of a carcinogen that becomes increasingly concentrated as it travels from the ileocecal valve to the rectum. (205 refs)

**78-0674 The Epidemiology of Oral Tumours.** (Eng) Lucas, R. B. (Dept. Oral Pathology, Royal Dental Hosp. London, Sch. Dental Surgery, 32 Leicester Square, London, WC 2, England). *Int Dent J* 27(3): 294-298; 1977.

The epidemiology of oral tumors is reviewed briefly. Since 90% of malignant oral tumors are squamous cell carcinomas, oral cancer and squamous cell carcinomas of the mouth are usually synonymous. The highest incidence of oral cancer is found in Hong Kong, and rates are generally high in Asiatic countries. It is not certain whether odontogenic tumors are linked to environmental causes or errors in the maturation of embryonic tissues. (7 refs.)

**78-0675 Time Trends: United States 1953-1973.** (Eng) Schneiderman, M. A. (Landow Room Building, 4C03, NCI, Bethesda, MD 20014). In: *Head and Neck Cancer. State of the Art Conference. February 16, 17 and 18, 1976.* (St. Louis, MO: Laryngoscope): Vol. 88, No. 1, Part 2, Suppl. 8, pp. 44-49; 1978.

Time-related changes in cancer incidence in the US are reviewed. Between 1935 and 1970, male mortality from cancer has increased, especially in nonwhites. The major single cause of this increase is smoking-related lung cancer. The lung cancer rate for women rose 11% between 1960 and 1974, mostly as a result of the increased number of female cigarette smokers. Cancer of the esophagus has increased substantially in nonwhites, but in whites there has been no increase and there may even be a decrease. It is suggested that dietary deficiencies, concomitant illnesses, or other factors are associated with these higher levels in blacks. For cancer of the nasopharynx, there has been a large increase in nonwhites, a smaller one in whites. The rate for women has not paralleled that for men. For laryngeal cancer, the increases have been larger in nonwhites than in whites. Data on occupation, chemical exposure, and smoking and drinking habits will probably shed more light on the etiology of these diseases. (no refs.)



## CHEMICAL CARCINOGENESIS

- 78-0676 **Mode of Action of Mycotoxins.** (Fre) Moule, Y. (Institut de Recherches Scientifiques sur le Cancer, 94800-Villejuif, France). *Pure Appl Chem* 49(11): 1733-1736; 1977.

Theories explaining the biochemical mechanism of the physiopathological effects induced by mycotoxins, particularly aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), are reviewed. In vivo studies demonstrate binding of AFB<sub>1</sub> to DNA and RNA macromolecules in different organs, particularly the liver. This binding can lead to errors of replication and mutagenesis, which may be responsible for the carcinogenicity of the mycotoxin. Active metabolites of AFB<sub>1</sub> have a direct effect on the enzyme repair system responsible for DNA repair in *Escherichia coli*, and errors in DNA repair may explain the mutagenicity of AFB<sub>1</sub>. If similar effects on the DNA enzyme repair system of eukaryotic cells can be demonstrated, the exact mechanism of the carcinogenicity of AFB<sub>1</sub> and other mycotoxins may be established. (33 refs.)

- 78-0677 **Absorption, Distribution and Excretion of [<sup>14</sup>C]Patulin by Rats.** (Eng.) Dailey, R. E. (Food and Drug Admin., 200 C St., SW, Washington, DC 20204); Blaschka, A. M.; Brower, E. A. *J Toxicol Environ Health* 3(3): 479-489; 1977.

Adult Sprague-Dawley rats were given a single po dose of the mycotoxin <sup>14</sup>C-patulin and sacrificed 4 hr to 7 days later. The treated mice had been exposed to daily po doses of unlabeled patulin (dissolved in pH 5.0 citrate buffer) in utero and for 41-66 wk after weaning. Controls were given the buffer only throughout gestation and for 38-81 wk after weaning. Approx 49% of the administered <sup>14</sup>C radioactivity was recovered from feces and 36% from urine within 7 days after dosing. Most of the labeled material was excreted within the first 24 hr. All of the <sup>14</sup>C activity detected in the urine samples represented metabolites and/or conjugates of the original <sup>14</sup>C-patulin. About 1%-2% of the total radioactivity was recovered as <sup>14</sup>CO<sub>2</sub> from expired air. <sup>14</sup>C-activity in various tissues and organs was determined throughout the 7-day period; the most significant retention site was the RBC. (16 refs.)

- 78-0678 **Carcinogen-Protein Complexes in Liver During Hepatocarcinogenesis by Aflatoxin B<sub>1</sub>.** (Eng) Mainigi, K. D. (Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA 19111); Sorof, S. *Cancer Res* 37(12): 4304-4312; 1977.

Male CDF rats were fed a diet containing Aflatoxin

B<sub>1</sub> (AFB<sub>1</sub>: 1 mg/kg) for 0, 4, 8, 16, or 24 wk or the same diet without carcinogen (control) for 24 wk. The rats were then given a single intragastric dose of <sup>3</sup>H-AFB<sub>1</sub> and sacrificed 18 or 48 hr later. The kinetics and relative amounts of labeled AFB<sub>1</sub>-protein complexes present in the liver cytosol were essentially unchanged throughout the carcinogen feeding period. At least eight macromolecular size classes of labeled complexes were separated by gel filtration, and their amounts and molecular wt were determined. In addition, one minor and three major weakly acidic classes and two weakly basic species of radioactive macromolecular complexes were resolved by chromatography involving ion exchange and molecular sieving. In contrast, direct incubation (2 hr, 1-4°C) of <sup>3</sup>H-AFB<sub>1</sub> at 1 x 10<sup>-7</sup> M with nonradioactive liver cytosols of rats fed the AFB<sub>1</sub> diet produced mainly one size class of labeled AFB<sub>1</sub> protein complexes with a modal molecular wt of 45,000-50,000 daltons, the molecular size of the complex classes present in greatest amount in vivo. These in vitro-generated complexes, assumed to result from hydrophobic associations, were distributed over the entire charge-size profile. In addition to macromolecular AFB<sub>1</sub> complexes, liver cytosols labeled in vivo or in vitro also had a radioactive nonmacromolecular AFB<sub>1</sub> adduct with an estimated mol wt of 500-5,000 daltons. The ability of AFB<sub>1</sub> metabolites to interact in vivo with a variety of liver proteins as well as extensively with DNA and RNA, suggests that the metabolites react nonspecifically with liver macromolecules generally. The carcinogenicity of AFB<sub>1</sub> may be due to its capacity to inflict multiple molecular insults on target cells. The presence of multiple AFB<sub>1</sub> macromolecular adducts during AFB<sub>1</sub> hepatocarcinogenesis complicates the problem of determining which carcinogen-protein interactions are important to the oncogenic process. (27 refs.)

- 78-0679 **Hepatic Uptake and Disposition of Aflatoxin B<sub>1</sub> in Isolated Perfused Rat Liver.** (Eng) Unger, P. D. (Dept. Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS 39216); Mehendale, H. M.; Hayes, A. W. *Toxicol Appl Pharmacol* 41(3): 523-534; 1977.

The hepatic uptake and disposition of aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) were determined in preparations of isolated, perfused, male Sprague-Dawley rat liver. During perfusion, 2.0 mg AFB<sub>1</sub>, or <sup>14</sup>C-AFB<sub>1</sub>, the approx LD50, were added to the blood. AFB<sub>1</sub> was rapidly removed from the perfusate by a monophasic process with a half-life of 18.6 min; by 5 min, >70% of the initial dose had been removed. By 4 hr, 28.9% of the total radioactivity from AFB<sub>1</sub> was excreted into the bile; only 0.26% of the total dose was excreted unchanged. Biliary excretion of AFB<sub>1</sub>-derived radioactivity and the parent compound



was greatest at 30 min, and the decay of radioactivity monophasic, with half lives of 47 and 25.33 min, respectively. Cholestasis was observed after 120 min of perfusion experiments and by 240 min in all experiments. Light microscopy observations, however, revealed no pathology. Concentration of AFB<sub>1</sub> in the bile was 32 times that in perfused plasma by 120 min. By 30 min, the bile concentration of AFB<sub>1</sub>-derived radioactivity not attributable to the compound reached a max of 314 times that in the plasma and six times that in the liver. Approx 95% of the dose was recovered. (23 refs.)

**80 In Vitro Metabolism of Aflatoxin B<sub>1</sub> by Rat Liver Nuclei.** (Eng) Vaught, J. B. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., New State Dept. Health, Buffalo, NY 14263); Klohs, W.; O'Hara, H. L. *Life Sci* 21(10): 1497-1504; 1977.

Metabolism of aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) in isolated Sprague-Dawley rat liver nuclei and microsomes was investigated. The rats either received no pretreatment or were inoculated ip with 30 mg/kg 3-methylcholanthrene (3-MC) for 3 consecutive days prior to sacrifice on day 4, or were inoculated with parabital (PB: 40 mg/kg on day 1, 48 mg/kg on day 2, 48 mg/kg on days 3-5) before sacrifice on day 6. The isolated nuclei metabolized AFB<sub>1</sub> to AFM<sub>1</sub>, AFQ<sub>1</sub>, and although the formation of AFP<sub>1</sub> was negligible. The metabolites formed were similar in both the nuclei and microsomal preparations, although the level of metabolism in microsomes was about 10% to 15% of the latter. PB pretreatment also increased the binding of AFB<sub>1</sub> metabolites to DNA and other macromolecules in the nucleus by a factor of 4. (29 refs.)

**81 Effect of Aflatoxin on the Humoral and Cell-Mediated Immune Systems of the Chicken.** Giambrone, J. J. (Dept. Avian Medicine, Coll. Veterinary Medicine, Univ. Georgia, Athens, GA, 30602); Ewert, R. D.; Wyatt, R. D.; Eidson, C. S. *Am J Vet Res* 39(2): 305-307; 1978.

White Leghorn chickens fed aflatoxin (2.5 µg/g diet) from age 2 to 4 wk or from hatching to age 4 wk were deficient in cell-mediated immunity, as measured by the graft-versus-rejection reaction. Delayed hypersensitivity reactions to tuberculin were also markedly reduced in chickens fed aflatoxin from hatching to age 4 wk. Although aflatoxin reduced serum titers of natural agglutinins to rabbit RBC only slightly, it significantly inhibited serum IgG and IgA production in birds fed aflatoxin diet from 0 to 4 wk or 2 to 4 wk of age. Aflatoxin administration from 0 to 2 wk of age had no residual effect on humoral immunity in 4-wk-old chickens. Thus, immunologic damage induced by aflatoxin is temporary. (5 refs.)

**78-0682 Inhibitors of Colon Carcinogenesis.** (Eng) Wattenberg, L. W. (Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN 55455); Lam, L. K.; Fladmoe, A. V.; Borchert, P. *Cancer* 40(5, Suppl): 2432-2435; 1977.

Doses of 0.2, 1.0, and 5.0 mg disulfiram (DS) and 0.3, 1.5, and 7.5 mg sodium diethyl-dithiocarbamate per gram of diet inhibited the carcinogenic effect of 1,2-dimethylhydrazine (DMH) in the large bowel of female CF<sub>1</sub> mice. Ethylene bis(dithiocarbamate)manganese and (5 mg/g) bis(ethylxanthogen) (1 and 5 mg/g) exerted a similar effect. DS or SDDC also inhibited the carcinogenic effect of axoxymethane, but to a lesser degree. Disulfiram may inhibit DMH metabolism at more than one step. (15 refs.)

**78-0683 The Effects of Iron Deficiency and the Quality and Quantity of Fat on Chemically Induced Cancer.** (Eng) Vitale, J. J. (Boston, MA, 02118); Broitman, S. A.; Vavrousek-Jakuba, E.; Rodday, P. W.; Gottlieb, L. S. *Adv Exp Med Biol* 91: 229-242; 1977.

The effects of iron deficiency and the quality and quantity of fat on 1,2-dimethylhydrazine (DMH)-induced cancer in male Lewis rats were investigated. Groups of 12 rats were fed either a whole-milk diet to produce Fe deficiency or a whole-milk diet supplemented with Fe (50 mg/kg diet). After 1 wk on the diets, half of the rats were treated with DMH (10 mg/kg sc, twice weekly). DMH-treated and untreated rats on the Fe-supplemented diet had no gross or microscopic abnormalities. Fe-deficient animals not given DMH had no neoplastic lesions. DMH-treated Fe-deficient animals developed neoplastic liver lesions within 4 mo. In another experiment, rats were fed various diets containing 20% safflower oil (saturated-fat diet) or 20% coconut oil (polyunsaturated diet). After 3 wk, half of the rats from each diet were given 10 mg/kg/wk DMH im for 20 wk. The diets were resumed for 15 more wk, and the animals were killed. The saturated-fat diets reduced the risk of colon cancer, but the unsaturated-fat diets promoted colon cancer. Tumors appeared after approximately 245 days (versus 126 days in Fe-deficient rats). Thus, dietary fat altered the site of DMH-induced carcinogenesis but Fe deficiency altered both latency period and the site. The latter effect could result from changes in the liver enzymes involved in the inactivation of DMH intermediates and/or aberrations in organelles within the hepatocyte involved in conjugation of DMH intermediates with glucuronic acid. (42 refs.)

**78-0684 Polyunsaturated Fat, Cholesterol and Large Bowel Tumorigenesis.** (Eng) Broitman, S. A. (Dept. Microbiology, Boston Univ. Sch. Medicine, 80 East Concord St., Boston, MA 02118); Vitale, J. J.; Vavrousek-



Jakuba, E.; Gottlieb, L. S. *Cancer [Suppl]* 40(5): 2455-2463; 1977.

The possibility that the disposition of cholesterol, which is influenced by the quality of dietary fat, may be associated with vascular lipidosis or colon cancer was evaluated. Sprague-Dawley CD rats were fed diets containing cholesterol plus (1) saturated fat, 20% coconut oil, to elevate serum cholesterol and promote vascular lipidosis or (2) polyunsaturated fat, 20% safflower oil, to minimize serum cholesterol elevations and retard the development of vascular lipidosis. The relationships of these diets to gastrointestinal tract tumors induced by 1,2-dimethylhydrazine (DMH: 10 mg/kg/wk, sc, for 20 wk) were studied. Serum cholesterol levels in rats fed diet 1 and given DMH were markedly elevated and were associated with moderate to severe vascular and aortic sudanophilia. Significantly, greater numbers of DMH-induced large bowel tumors were found in the rats fed diet 2 than in those fed diet 1. It is suggested that the polyunsaturated fat diet promoted the decrease in serum cholesterol levels concomitant with an increase in fecal neutral and acid sterols, which in turn augmented DMH tumorigenesis. Thus, in the animal model used, the interaction of dietary fat (quality or quantity) with endogenous or dietary cholesterol determined whether diet will contribute to the development of vascular lipidosis or augmentation of small and large bowel tumorigenesis. (39 refs.)

78-0685 **An Organ Culture Method for Adult Colon from Germfree and Conventional Mice: Effects of Donor Age and Carcinogen Treatment on Epithelial Mitotic Activity.** (Eng) Defries, E. A. (Dept. Cellular Pathology, Imperial Cancer Res. Fund, Post Office Box No. 123, Lincoln's Inn Fields, London WC2A 3PX, England); Franks, L. M. *J Natl Cancer Inst* 58(5): 1323-1328; 1977.

Epithelial mitotic activity was studied in adult mouse colon maintained in culture for several weeks by the use of Waymouth's MB 752/1 medium supplemented with 10% calf serum. No differences in mitotic activity were detected in colon explants from germfree C57BL mice that were 5 wk, 5 mo, or 9 mo old. The effects of old age on mitotic activity were not determined, since colon epithelium from 30-mo-old conventional C57BL mice could not be maintained in culture. Colon explants from conventional mice treated for 32 wk with the carcinogen 1,2-dimethylhydrazine (8.25 mg/wk, sc) appeared to have a higher potential for mitotic activity in vitro than those from age-matched, untreated controls. However, the difference was significant only at the 10% level. The ultrastructure of the epithelial cells was normal, indicating that the organ culture system may be useful for studying the direct effects of carcinogens and other agents on adult colon epithelium. (18 refs.)

78-0686 **Studies on *Agrobacterium tumefaciens*. V. Avirulence Induced by Temperature and Ethidium Bromide.** (Eng) Lin, B. C. (Biology Res. Center, Academia Sinica, Nanking, Taipei, Taiwan); Kado, C. I. *Can Microbiol* 23(11): 1554-1561; 1977.

When tumorigenic *Agrobacterium tumefaciens* strains were subcultured at temperatures between 31.5 and 37 C or in broth containing ethidium bromide, they lost their capacity to induce tumors in tomato plants. The loss of virulence depended on cell population density; 100 cells/ml were more sensitive to treatment than 10<sup>6</sup> cells/ml. Virulent strains made avirulent by temperature or ethidium bromide treatment still harbored a large plasmid of 70-80 megadaltons compared with the 100-120-megadalton plasmid in the untreated strains. Thus, the loss of virulence may not require total loss of the virulence-specifying plasmid, but may result from loss of only a small segment. (22 refs.)

78-0687 **Electron Microscopic Observations on the Experimental Granuloma of Rabbit Lung Induced by a Toxic Glycolipid (Cord Factor) from *Mycobacterium tuberculosis*.** (Eng) Nishi, K. (Res. Inst. Tuberculosis, Toneyama Natl. Hosp., Toyonaka, Japan); Yamagata, H. *Electron Microsc (Tokyo)* 26(3): 231; 1977. (no refs.)

78-0688 **Granuloma Formation in Lungs of Mice after Intravenous Administration of Emulsion of Trehalose-6,6'-Dimycolate (Cord Factor): Reaction Intensity Depends on Size Distribution of the Oil Droplets.** (Eng) Yokoi, E. (Lab. Immunobiology, NCI, Bethesda, MD 20001); Rapp, H. J. *Infect Immun* 18(2): 552-554; 1977.

Granuloma formation was studied in NIH Swiss mice following iv injection of 2 µg/ml trehalose-6,6'-dimycolate (TDM) in 1% oil and 0.2% Tween 80. Emulsions prepared by grinding alone, rather than by ultrasonic treatment or by combination of the two procedures, produced by far the greater number of tumors. This response was attributed to the size distribution of oil droplets, which were greatest in this emulsion. The correlation between the antitumor activity of emulsified TDM and the intensity of its granulomatous activity is under further study. (19 refs.)

78-0689 **Carcinogenic Effects of Niridazole on Rodents Infected with *Schistosoma mansoni*.** (Eng) Bulay, O. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105);



n, H.; Clayson, D. B.; Shubik, P. *J Natl Cancer Inst* 59(6): 15-1630; 1977.

carcinogenicity of 1-(5-nitro-2-thiazolyl)-2-diazolidinone (niridazole), a widely used schistosomicide, was examined in Swiss mice and Syrian golden hamsters. *Schistosoma mansoni* infection was evaluated as a cofactor. Mice fed niridazole developed a high incidence of neoplasms in the forestomach, lungs, mammary glands, urinary tract, and ovaries. Tumors of the forestomach and urinary tract were found in hamsters. Infection with schistosomes had no apparent influence on tumor incidence. The results indicated the need for reevaluation of the possible carcinogenicity of this drug in man. (30 refs.)

0690 Separation and Identification of Metabolites of the Arylamide, N-3-fluorenyl-acetamide, by High-Pressure Liquid Chromatography. (Eng) Gutmann, H. Lab. Cancer Res., Veterans Admin. Hosp., Minneapolis, MN 55417; Kaplan, E. *J Chromatogr* 144(1): 136-140; 1977.

Metabolites of N-3-fluorenyl-acetamide in rat and guinea pig liver microsomal preparations were identified as N-(3-acetamido)fluoren-9-ol and N-(3-acetamido)fluoren-9-one by high-pressure liquid chromatography. The retention times of the metabolites and those of N-fluoren-2-yl-acetamide are compared. (12 refs.)

0691 Report on Bioassay of Tolbutamide for Possible Carcinogenicity. (Eng) Fredrickson, D. S. H. Bethesda, MD 20014. *Fed Regist* 42(237): 62212; 1977.

carcinogenicity of tolbutamide in Fischer 344 rats and 3F1 mice was investigated. The animals were given 0, 100 or 24,000 ppm (rats) or 25,000 or 50,000 ppm (mice) tolbutamide in the diet five times a week for 78 wk and then observed for 24-28 wk. Survival was not affected by this treatment, and there was no statistically significant incidence of neoplasms compared to untreated controls. It is concluded that tolbutamide is not carcinogenic to rats and mice at these doses. (no refs.)

0692 Selection of an In Vitro Carcinogenicity Test for Derivatives of the Carcinogen Hexamethylphosphoramide. (Eng) Ashby, J. (Imperial Chemical Industries Limited, Central Toxicology Lab., Alderley Park, Macclesfield, Cheshire, England); Styles, J. A.; Anderson, D. *Br J Cancer* 36(5): 564-571; 1977.

The carcinogenicity of hexamethylphosphoramide (HMPA) and three of its analogs was evaluated in the Ames *Salmonella typhimurium* mutation assay and the Styles cell transformation assay. The analogs were the related leukemogen phosphoramidate, the putative noncarcinogen phosphoric trianilide, and N,N,N''-trimethylphosphorothioic triamide, a compound of unknown and hitherto unpredictable properties. While both tests found the trianilide negative, the Ames test failed to detect phosphoramidate as positive and gave an erratic and predominantly negative response to HMPA. In contrast, the transformation assay in BHK cells found both phosphoramidate and HMPA positive. This test-response profile indicates that the transformation assay is the preferred test with which to evaluate analogs of HMPA for potential carcinogenicity. Some structural requirements for potential carcinogenicity within this class of compounds are tentatively deduced. (21 refs.)

78-0693  $\beta$ -Glucuronidase Activity in Peripheral Blood Leukocytes of Rats Following Subacute Benzene Vapor Poisoning. (Pol) Moszczynski, P. (I Oddzial Chorob Wewnetrznych AOA w Brzesku, skr. poczt. 13, 30-969 Cracow 28, Poland); Starek, A. *Med Pr* 28(4): 249-256; 1977.

A determination was made of the effect of exposure to concentrated benzene vapor (27,000 mg/m<sup>3</sup>, 6 hr/day for 10 consecutive days) on  $\beta$ -glucuronidase (GU) activity in the peripheral blood neutrophils and lymphocytes of Wistar rats. Following exposure, there was a statistically significant reduction in the number of granulocytes and lymphocytes; GU activity was fivefold lower than preexposure values. However, the percentage of GU-positive cells was unchanged. The proportion of individual types of enzyme-positive cells was altered; ie, granular lymphocytes decreased, but granular diffuse lymphocytes increased. It is concluded that benzene exerts a depressive effect on granulocytes, but it increases the lability of the membranes of the lymphocytes. (19 refs.)

78-0694 Changes of the Endoplasmic Reticulum in the Hepatic Parenchymal Cell of 0.6% 3'-MeDAB-fed Guinea Pigs (Meeting Abstract). (Eng) Tsuchiya, A. (Sch. Medicine, Toyama Medical Pharm. Univ., Toyama, Japan); Ogawa, K. *J Electron Microscop* (Tokyo) 26(3): 299; 1977. (no refs.)

78-0695 Formation of Blastomogenic Diphenylamino Derivatives as a Result of Direct Azo Dye Metabolism. (Rus) Genin, V. A. (Oncological Res. Center, Acad. Medical Sciences USSR, Moscow, USSR). *Vopr Onkol* 23(9): 50-52; 1977.



Urine samples from 22 male and female workers (equipment operators, packers, and maintenance mechanics in drying and grinding operations) exposed occupationally to direct azo dyes (Direct Black 3, Direct Diazo Black, Direct Pure Blue, and Direct Light Fast KU) for 4-30 yr were analyzed for blastomogenic diphenylamino derivatives of the dyes. Benzdine was found in eight subjects, dianisidine in three; the concentrations reached up to 0.3 mg/liter. During an observation period of several years, urinary bladder tumors were found in three workers aged 68, 70, and 72 yr with respective latency periods of 18, 33, and 43 yr. The length of occupational exposure to the dyes was 3, 18, and 24 yr, respectively. The findings indicate that the metabolism of direct azo dyes to blastomogenic free diphenylamino derivatives is one of the principal etiologic factors of urinary bladder tumor in exposed workers. (7 refs.)

- 78-0696 The Mutagenic Assay of Some Hair Dye Components, Using the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells.** (Eng) Palmer, K. A. (Genetic Toxicology Branch, Div. Toxicology, Food and Drug Admin., Washington, DC); Denunzio, A.; Green, S. *J Environ Pathol Toxicol* 1(1): 187-191; 1977.

The mutagenicity of five hair dye components was tested at the thymidine kinase +/- locus of L5178Y mouse lymphoma cells. The assay was carried out in vitro, without metabolic activation, during a 24-hr chemical exposure period. Three of the components, m-phenylenediamine, 2-nitro-p-phenylenediamine, and 4-nitro-o-phenylenediamine, gave a positive dose-related response; 2,4-diaminoanisole gave a questionable response; and 2,5-diaminoanisole gave a negative response. It is concluded that further in vivo tests are necessary to establish the safety of hair dyes. (9 refs.)

- 78-0697 Effect of Repeated Applications of Two Semipermanent Hair Dyes to the Skin of A and DBA/Mice.** (Eng) Searle, C. E. (Dept. Cancer Studies, Univ. Birmingham, Medical Sch., Birmingham B15 2TJ, England); Jones, E. L. *Br J Cancer* 36(4): 467-478; 1977.

The effect of topical application of two semipermanent (nonoxidizing) hair dyes to male and female albino A/Ber and DBA/Mice was investigated. One volume of dye was diluted with four parts of deionized water and five parts of acetone and applied directly to the skin. The amount applied was 0.4 ml per application; this was reduced to 0.2 ml at 24 wk for DBA/Mice because of toxicity. There were 138 applications over 80 wk. The toxicity in the DBA/Mice was centered in the urogenital tract; three mice had squamous papillomas near the penis. Compared with controls, the incidence of lymphoid tumors in treated DBA/Mice was statisti-

cally significant, 8/62 mice, and these tumors occurred earlier than those in controls. Two fibrosarcomas of the u and six ovarian tumors were also found in the DBA/Mice. Compared with controls (13 tumors) the number of tumors in treated strain A mice (29 tumors) was not significantly different. The main difference between the strains was the tumors tended to appear earlier in A mice. (25 refs.)

- 78-0698 Urinary Bladder Tumors in Dogs Given 4,4'-Methylene-bis(2-chloroaniline) (MOCA).** (Eng) Stula, E. F. (Haskell Lab. Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Incorporated, Wilmington, DE); Barnes, J. R.; Sherman, H.; Reinhardt, F.; Zapp, J. A. *J Environ Pathol Toxicol* 1(1): 31-50; 1977.

Six female beagle dogs were given a daily po dose of 10 mg/kg of 4,4'-methylene-bis(2-chloroaniline) (MOCA), 3 days/week for the first 6 wk and then 5 days/week for up to 9.0 yr. The dose varied from 3 to 15 mg/kg/day. Six female beagle dogs were kept as untreated controls. The av plasma glutamic-pyruvate transaminase activity of the dogs fed MOCA was higher than that of the controls during the first and last 2 yr. During the eighth and ninth years, the urine sediment from MOCA dogs contained excessive numbers of RBC, WBC, and epithelial cells. Some epithelial cells contained abnormalities that suggested neoplasia in the genitourinary tract. One dog sacrificed after 8.3 yr had a papillary transitional cell carcinoma of the urinary bladder. Of four dogs sacrificed after 9.0 yr, three had papillary transitional cell carcinomas of the bladder; one had a combined transitional cell carcinoma and adenocarcinoma of the urethra. The urethral tumor metastasized to the liver, but the papillary transitional cell carcinoma did not invade the muscle layers of the bladder wall and did not metastasize. Since no urinary bladder tumors were found in the six controls, MOCA was considered to be a urinary bladder carcinogen under the conditions employed. Hyperplastic nodules were present in 3/5 MOCA dogs but they were not found in the controls. (19 refs.)

- 78-0699 Inhibitor Effect of Ellipticine (Dimethyl-5,11-(6H)pyrido(4,3-b)carbazole) on Liver Carcinogenesis Induced by BT6(N,N-dimethyl-2-benzothiazolylazo)aniline): Incidences on Cytoc P450 and Arginase Activity (Meeting Abstract).** Truhaut, R. (Laboratoire de Toxicologie, Faculté de Pharmacie, 4 Avenue de l'Observatoire, Paris, France); Dophuoc, H.; Nguyen, B. G. In: *Fourth Meeting of the European Association for Cancer Research, 13-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 86; 1977.



**7700 Mutagenic Effect of New Chemical Compounds. IV. The Effect of Dialkylaminoethyl Esters of Dihydro-7H-benz(a)carbazole Carboxylic Acids.** (Rus)

Onikyan, G. M. (A. L. Mndzhoyan Inst. Fine Organic Chemistry, Erevan, USSR); Akopyan, L. G.; Darbinyan, G. Tumasyan, E.A. *Genetika* 13(9): 1621-1625; 1977.

The mutagenic activity of a series of four dialkylaminoethyl esters of 5,6-dihydro-7H-benz(a)carbazole carboxylic acids was assessed in a threonine-, leucine-, and vitamin B<sub>12</sub>-deficient strain of *Escherichia coli* and a lysine-deficient, streptomycin-sensitive strain of *Actinomyces rimosus*. All compounds induced reverse mutations. The highest mutagenic activity was detected for the derivative with a substituted aminoether group in position 9. The frequency of reverse mutations in the threonine locus in *E. coli* and the lysine locus in *A. rimosus* was, respectively, 1,575 and 1,240 times higher than that in controls and 4.31 and 4.48 times higher than that after exposure to ethyleneamine. (4 refs.)

**7701 Lung Cancer Following Exposure to Bis(chloromethyl)ether: A Case Report.** (Eng) Reznik, S.

Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Wagner, H. H.; Atay, Z. *J Environ Health Toxicol* 1(1): 105-111; 1977.

A 55-yr-old man died of metastatic pulmonary adenocarcinoma 12-yr after 2 yr inhalation exposure to high levels of bis(chloromethyl)ether and chloromethyl methyl ether, reaction by-products in his experiments. The literature is briefly reviewed. (20 refs.)

**7702 Mortality of Workers Exposed to Chloroprene.** (Eng) Pell, S. (Medical Div., E.I. du Pont de Nemours and Co., Wilmington, DE, 19898). *J Occup Med* 21:29; 1978.

In an investigation of the possible relationship between chloroprene exposure and lung cancer, the numbers of lung cancer deaths were determined in two groups of workers: 270 men exposed between 1931 and 1948 and 1,576 men exposed between 1942 and 1957. There were 3 lung cancer deaths in the first group and 16 in the second, numbers that would be expected in a nonexposed population. Among maintenance mechanics in the second group, there were eight lung cancer deaths (4 living and 4 dead). A crude morbidity analysis suggested that this group had an excess lung cancer incidence, but the absence of excess mortality in other high-exposure occupational groups indicates that chloroprene does not increase the risk of lung cancer. (9 refs)

**7703 Covalent Binding of the Carcinogen Trichloroethylene to Hepatic Microsomal Proteins and**

**to Exogenous DNA In Vitro.** (Eng) Banerjee, S. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016); Van Duuren, B. L. *Cancer Res* 38(3): 776-780; 1978.

The metabolism of 1,2,2-trichloroethylene (TCE) in species that develop liver tumors following exposure to this carcinogen (B6C3F<sub>1</sub> hybrid mice) was compared with that in species resistant to TCE tumor induction (Osborne-Mendel rats). Hepatic microsomes from male B6C3F<sub>1</sub> mice covalently bound 46% more TCE than did microsomes from Osborne-Mendel rats. Furthermore, 30% more TCE was bound to microsomes from mature male Sprague-Dawley rats than immature rats of the same strain. Binding to microsomal protein was 44% and 63% higher in 5- to 9-wk-old Sprague-Dawley rats than in Osborne-Mendel and Fischer rats of the same age. There was 29% more binding to proteins from male Osborne-Mendel rats than from females. In B6C3F<sub>1</sub> mice TCE bound to stomach, lung, and kidney microsomes as efficiently as to liver microsomes; microsomes from female lung bound 18% more TCE than those from male lung. TCE also covalently bound to DNA, but only in the presence of microsomes. Thirty-seven percent more TCE bound to microsomal protein from male mice than that from female mice, and binding to DNA was 160% greater in the presence of the male microsomes. In vivo pretreatment of mice with 100 mg/kg sodium phenobarbital enhanced TCE binding to microsomal protein and DNA by 58% and 41%, respectively. In vitro treatment with 30 mg/kg 3-methylcholanthrene increased binding to protein by 31%. At 1.2 mM, trichloropropene oxide increased TCE binding to protein and DNA by 15%; at concentrations > 1.2 mM, however, the amount of TCE bound to protein decreased, but there was a constant increase in the binding of TCE to DNA. (30 refs)

**78-0704 Lysine Transfer RNA<sub>2</sub> Is the Major Target for L-Ethionine in the Rat.** (Eng) Kuchino, Y. (Biology Div., Natl. Cancer Center Res. Inst., Tsukiji-5-1-1 Chuo-ku, Tokyo, Japan); Sharma, O. K.; Borek, E. *Biochemistry* 17(1): 144-147; 1978.

The labeling of rat liver transfer RNA (tRNA) by the hepatocarcinogen ethionine was investigated in three female Holtzman rats inoculated ip with 0.5 mCi of L-[ethyl-<sup>3</sup>H]ethionine. Following a 24-hr fast, the rats were sacrificed and the hepatic tRNA was examined. Reverse-phase column chromatography of the tRNA species indicated that approx 50% of the radioactivity was eluted with the lysine peak. Cochromatography revealed that tRNA<sup>Lys</sup>, and not the Lys<sub>1</sub> species contained the radioactivity. It is not known if there is a causal relationship between this specific alkylation and the carcinogenicity of ethionine. (24 refs.)

**78-0705 Mutagenic Activity of Thiocarbamate Herbicides in *Salmonella typhimurium*.** (Eng) Sikka, V.



H. C. (Life Sciences Div., Syracuse Res. Corp., Merrill Lane, Univ. Heights, Syracuse, NY, 13210); Florczyk, P. *J Agric Food Chem* 26(1): 146-148; 1978.

Three thiocarbamate herbicides, S-(2,3-dichloroallyl)diisopropylthiocarbamate (diallate), S-(2,3,3-trichloroallyl)diisopropylthiocarbamate (triallate), and 2-chloroallyl-N,N-diethylthiocarbamate (CDEC), were tested for their mutagenicity in *Salmonella typhimurium* strains TA100, TA1535, TA98, and TA1538 with and without an S-9 rat liver microsomal activation system. All herbicides showed significant mutagenic activity in strains TA1535 and TA100, but only in the presence of the S-9 fraction. Mutations were not induced in TA98 and TA1538 at any time. This specificity suggested that base-pair and not frameshift mutations were induced. Diallate was the most effective of the three pesticides in inducing mutations. The lower activity of triallate and CDEC could be due to a lesser degree of metabolic transformation, poor solubility of the herbicides and/or their metabolites in agar, or their low permeability in the bacterial cells. At concentrations above 100, 500, and 50 µg/plate for diallate, triallate, and CDEC, respectively, the number of revertants decreased, probably as a result of toxicity. The mechanism by which these compounds induce mutations is unknown. (15 refs)

**78-0706 The Influence of Nutritional Factors on Pulmonary Adenomas in Mice.** (Eng) French, F. A. (Mount Zion Hosp. and Medical Center, San Francisco, CA, 94115). *Adv Exp Med Biol* 91: 281-292; 1977.

Studies of the effects of nutritional factors on pulmonary adenoma development in A/He mice treated with urethane (1,000 mg/kg ip) are reviewed. Protracted posttreatment with nicotinamide (0.25%, 0.4%, 2.0%), choline dihydrogen citrate (2.5%, 0.25%), choline bitartrate (2.5%), or myo-inositol (0.25%, 4.0%) significantly reduced the mean number of lung tumors per mouse. The effect of nicotinamide was specific and not shared by nicotinic acid. Seventeen other vitamins or vitaminlike factors, including betaine and methionine, were not tumor inhibitory. The mechanism of action of choline and inositol are unknown, but the carcinostatic activity of nicotinamide is probably due to its inhibition of tumor-derived transfer RNA methylase. (23 refs.)

**78-0707 In Vitro Transformation of Human Cells by N-Hydroxyurethane and Urethane-DNA Complex.** (Eng) Talageri, V. R. (Biology Div., Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay-400 012, India); Bhide, S. V.; Ranadive, K. J. *Indian J Cancer* 14(3): 216-224; 1977.

A single 72-hr exposure of normal human fetal fibroblasts to N-hydroxyurethane (10 mg/ml medium) or urethane-DNA complex (1 mg/ml medium) brought about changes in the

morphological, cytological, and biochemical profiles of cells. In vitro malignant transformation was evidenced by infinite life-span, ability to produce tumors in hamster cheek pouches, and increased aldolase and lactic dehydrogenase activities. Untreated and control DNA-treated cells, which had a diploid stem-line and normal enzyme levels, had a limited life-span of 15-20 passages before degeneration. (36 refs)

**78-0708 Morphology of Experimental Pulmonary Tumors in Albino Rats and Syrian Hamsters.** (Rus) Vysamyae, A. I. (Inst. Experimental and Clinical Medicine, Tallin, USSR). *Vestn Akad Med Nauk SSSR* 77-79; 1978.

The incidence and histology of pulmonary neoplasms were studied in random-bred and Wistar albino rats and in Syrian hamsters exposed to various chemical carcinogens. Chronic administration of ethylurethane (50 mg, 3x/wk) induced bronchial lung tumors in 9/145 rats. Histologically, 7 tumors were alveolar adenomas and 2 were keratinizing epidermoid tumors. Combined peroral administration of urethane and repeated intratracheal instillations of soot produced lung tumors in 18/287 rats (8 alveolar adenomas, 1 bronchogenic and bronchiogenic adenoma, 1 malignant and 3 benign epidermoid tumors, 1 fibrosarcoma, and 3 multiple pulmonary hemangiomas). Intratracheal administration of benzo(a)pyrene (50 mg/day, 3x/wk) in various suspensions produced epithelial tumors in 21/39 rats. Prolonged administration of diethylnitrosoamine (DENA: po or sc) to hamsters resulted in a large number of upper respiratory tract tumors (primarily, tracheal papillomas). (11 refs.)

**78-0709 Diaplacental Carcinogenesis: Tumor Localization and Tumor Incidence in NMRI Mice after Diaplacental Initiation with DMBA and Urethane and Postnatal Promotion with the Phorbol Ester TPA in a Modified 2-Stage Berenblum/Mottram Experiment.** (Eng) Goertt, K. (Inst. Experimental Pathology, German Cancer Research Center, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, Germany); Lohrke, H. *Virchows Arch [Pathol Anat]* 376: 117-132; 1977.

The results of postmortem examinations of NMRI mice subjected to a two-stage Berenblum/Mottram (initiation/promotion) experiment, i.e., transplacental initiation with 7,12-dimethylbenz(a)anthracene (DMBA: 4 or 5 daily doses of 15 or 30 mg/kg po) or urethane (U: 3 daily doses of 60 mg/kg ip) and postnatal promotion with 12-tetradecanoylphorbol-13-acetate (TPA), are reported. DMBA and U were administered between gestation days 10 and 21. In the second stage, TPA was applied to the back skin of the 12- to 36-wk-old mice twice daily for a total of 48 applications of 0.00615 mg/0.1 ml acetone. Within the 52-wk experimental period, treatment with DMBA + TPA



U + TPA led to the formation of a broad spectrum of benign and malignant tumors on the back skin and in other tissues and organs. However, skin carcinomas developed exclusively after combined treatment (DMBA + TPA and U + TPA). In general, tumor yield with the combined treatment considerably exceeded that due to spontaneous formation and that produced by initiation alone. U was a less effective initiator than DMBA. Postmortem examinations showed that TPA was able to activate initiated tumor cells in internal organs to form tumors. Thus, after local absorption, TPA must have reached the lymphatics and blood vessels and subsequently been distributed throughout the body. The skin and liver were most susceptible to the combined treatment, which also significantly stimulated tumor growth in organs that tend to show spontaneous tumors. The preferential occurrence of genital tract tumors in females points to a possible hormonal involvement. The relevance of this finding to naturally induced tumors in human pathology is discussed. (refs.)

**7710 Prostaglandins and Skin Tumor Promotion: Inhibition of Tumor Promoter-induced Ornithine Decarboxylase Activity in Epidermis by Inhibitors of Prostaglandin Synthesis.** (Eng) Verma, A. K. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Rice, H. M.; Boutwell, R. K. *Biochem Biophys Res Commun* 79(4): 1166; 1977.

The effect of various inhibitors of prostaglandin synthesis on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity in female Charles River CD-1 mice was investigated. The TPA, prostaglandin, and test compounds were dissolved in acetone and applied individually to shaved areas of the mouse dorsal skin in a volume of 0.2 ml. Application of 10 nanomoles (nmol) TPA increased ODC activity to a level 200 times higher than that of control mice by 4-8 hr. Treatment of the mouse skin with 280 nmol indomethacin 2 hr prior to TPA suppressed this activity to 10%. The suppression was dose-dependent. Enzyme induction was also suppressed significantly by 1,000 nmol acetylsalicylic acid and 570 nmol flufenamic acid; dexamethasone had no effect. The inhibitory effect of indomethacin was overcome when either prostaglandin  $E_1$  or  $E_2$  was applied concurrently with TPA. Treatment of mouse skin with prostaglandin  $E_2$  alone did not increase epidermal ODC activity measurably, but in some experiments, prostaglandin  $E_2$  applied concurrently with TPA resulted in a significant increase in enzyme induction over the level obtained with TPA alone. (refs.)

**7711 Inhibition of 12-O-Tetradecanoylphorbol-13-acetate-induced Ornithine Decarboxylase Activity in Mouse Epidermis by Vitamin A Analogs (Retinoids).** Verma, A. K. (McArdle Lab. Cancer Res., Univ. Wis-

consin, Madison, WI, 53706); Rice, H. M.; Shapas, B. G.; Boutwell, R. K. *Cancer Res* 38(3): 793-801; 1978.

The ability of 23 synthetic retinoids to inhibit 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced epidermal ornithine decarboxylase (ODC) activity and affect the TPA-induced accumulation of polyamines in female Charles River CD-1 mouse epidermis was investigated. The retinoid to be tested was applied to the skin 1 hr before topical application of 17 nanomoles (nmol) TPA; ODC activity was measured 4.5 hr later.  $\beta$ -Retinoic acid,  $\alpha$ -retinoic acid, 13-cis-retinoic acid, 13-cis-retinal, and 5,6-dihydroretinoic acid, as well as the dimethylmethoxyethylcyclopentenyl and dimethylacetyl-cyclopentenyl analogs of retinoic acid gave 50% inhibition with <1-nmol applications. Replacement of the cyclohexenyl ring of  $\beta$ -retinoic acid with a substituted phenyl ring decreased its activity; approx 14 nmol of the trimethylmethoxyphenyl analog of either retinoic acid or ethyl retinoate were required for 50% inhibition. The trimethylhydroxyphenyl analog of ethyl retinoate, the trimethylmethoxyphenyl analog of N-ethylretinamide, and the phenyl analog of retinoic acid had minimal activity. Application of 0.21 nmol of the 8-fluorotrimethylmethoxyphenyl analog of methyl retinoate and 5 nmol of the 12-fluorotrimethylmethoxyphenol analog of ethyl retinoate resulted in 50% inhibition of ODC activity. The 13-trifluoromethyltrimethylmethoxyphenyl analog of ethyl retinoate was devoid of inhibitory potency. A similar inhibition of enzyme activity was observed when these retinoids were administered systemically. Furthermore, the active analogs inhibited the phorbol ester-induced accumulation of epidermal putrescine without affecting the levels of spermidine, spermine, and S-adenosyl-L-methionine decarboxylase. ODC inhibition by these retinoids may be a good in vivo test of their prophylactic activity. (49 refs)

**78-0712 Effects of Tumor Promoters and Steroidal Anti-inflammatory Agents on Skin of Newborn Mice In Vivo and In Vitro.** (Eng) Slaga, T. J. (Biology Div., Post Office Box Y, Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Lichti, U.; Hennings, H.; Elgjo, K.; Yuspa, S. H. *J Natl Cancer Inst* 60(2): 425-431; 1978.

In adult mice, the phorbol esters 12-O-tetradecanoylphorbol-13-acetate (TPA) and 12-O-hexadecanoylphorbol-13 acetate (HPA) are not only potent tumor promoters, but also potent stimulators of epidermal DNA synthesis and ornithine decarboxylase (ODC) activity. However, when applied topically to newborn BALB/c mice, TPA and HPA had essentially no effect on epidermal and dermal DNA synthesis or on epidermal ODC activity. Exposure of primary cultures of newborn mouse epidermal cells to TPA or HPA markedly stimulated both DNA synthesis and ODC activity. The anti-inflammatory steroids dexamethasone and fluocinolone acetonide (FA) were potent inhibitors of tumor promotion and epidermal DNA synthesis in adult mice. However, when applied topically in newborn mice, FA stimulated epidermal



or dermal DNA synthesis approx twofold at 48 hr posttreatment. In primary cultures of epidermal cells from newborn mice, dexamethasone or FA caused an early stimulation of DNA synthesis followed by a 50% inhibition of DNA synthesis 2-3 days after a 1 hr pulse treatment. Also, DNA synthesis was moderately inhibited when FA was added to primary cultures of dermal fibroblasts. These results suggest that newborn mouse epidermal cells grown in vitro acquire the biologic properties of adult mouse epidermis. These specialized functions may be associated with membrane changes, and they do not appear to be mediated through the dermis. (30 refs.)

- 78-0713 Structure and Tumor-promoting Activity of Analogues of Anthralin (1,8-Dihydroxy-9-anthrone).** (Eng) Van Duuren, B. L. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY 10016); Segal, A.; Tseng, S. S.; Rusch, G. M.; Loewengart, G.; Mate, U.; Roth, D.; Smith, A.; Melchionne, S.; Seidman, I. *J Med Chem* 21(1): 26-31; 1977.

Seventeen analogs of the tumor-promoting agent anthralin were tested for biological activity in female ICR/Ha Swiss mice who received a single cutaneous application of 20  $\mu$ g 7,12-dimethylbenz(a)anthracene in 0.1 ml acetone followed 2 wk later by applications of the test compounds in 0.1 ml acetone three times a week. 1,8-Dihydroxy-10-acetyl-9-anthrone (15  $\mu$ g), 1,8-dihydroxy-10-myristoyl-9-anthrone (300  $\mu$ g), 1-hydroxy-9-anthrone (80  $\mu$ g), and juglone (62  $\mu$ g) demonstrated tumor-promoting activity. 1,8-Diacetoxy-9-anthrone (124  $\mu$ g), 1-hydroxyanthracene (80  $\mu$ g), and acetyl-juglone (76  $\mu$ g) showed marginal activity. At least one phenolic hydroxyl group hydrogen bonded to the C-9 carbonyl oxygen and one benzylic proton at the C-10 position were concluded to be necessary for promotional activity. The chelating properties of anthralin and the inactive analog 1,8-dihydroxyanthraquinone were tested with bivalent metals, and no difference was detected. (28 refs.)

- 78-0714 Effect of Aging in Two-Stage Carcinogenesis on Mouse Skin with Phorbol Myristate Acetate as Promoting Agent (Letter to Editor).** (Eng) Van Duuren, B. L. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016); Smith, A. C.; Melchionne, S. M. *Cancer Res* 38(3): 1-2; 1978.

Life-table analysis curves were constructed for the results of a previous experiment in which 7,12-dimethylbenz(a)anthracene (DMBA: 20  $\mu$ g/0.1 ml acetone) was applied in a single dose to the dorsal skin of female ICR/Ha mice, followed at various intervals by the promoter phor-

bol myristate acetate (PHA: 2.5  $\mu$ g/0.1 ml acetone, 3x for life). Tumors first arose between 4 and 9 wk after beginning of promotion. However, the percentage of tumor bearers decreased with increasing age of the animals at onset of promotion. Furthermore, tumor yield decreased when there was a long interval between initiation and promotion or when both initiation and promotion occurred in animals. The av number of tumors per tumor bearer decreased with increasing age at the onset of promotion (refs)

- 78-0715 Age-related Modification of 7,12-Dimethylbenz[a]anthracene Binding to Rat Mammary Gland DNA.** (Eng) Janss, D. H. (Endocrine Carcinogenesis Section, NCI Frederick Cancer Center, Frederick, MD 21701); Ben, T. L. *J Natl Cancer Inst* 60(1): 173-177; 1978.

Modifications of the binding of 7,12-dimethylbenz[a]anthracene (DMBA) to female Sprague-Dawley rat mammary gland and liver DNA were investigated following a single po dose of 12.5 mg/kg DMBA at 35, 50, or 120 days of age. DMBA binding to mammary DNA was dependent on the age of the animal at the time of carcinogen administration: compared with results from 50-day-old rats, binding in the 35-day-old animals was less, by an av of 52% at all times, while depression averaged about 77% at all times for day-old rats. In contrast, the pattern of binding to liver DNA was similar in all three age groups; furthermore, the amount of DMBA bound appeared to be a function of the amount of carcinogen administered. The amount of binding to liver DNA was also significantly lower than that to mammary DNA throughout the experiment. The incidence of mammary tumors in 50-day-old animals increased from 100% as the amount of DMBA administered was raised from 5 to 20 mg. Over this range, the ratio of DMBA administered to DMBA bound remained constant; this was not observed in the 35- or 120-day-old groups. These findings reveal a significant correlation between the age of the rat, the amount of DMBA bound to DNA, and the incidence of mammary tumors following DMBA feedings. (30 refs.)

- 78-0716 Differences Between Products of Binding of 7,12-Dimethylbenz(a)anthracene to DNA in Mouse Skin and in a Rat Liver Microsomal System.** Bigger, C. A. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701); Tomaszewski, J. E.; Dipple, A. *Biochem Biophys Res Commun* 80(1): 229-235; 1978.

The products of 7,12-dimethylbenz(a)anthracene (DMBA) DNA binding in female NIH Swiss mouse skin in vivo and a male Sprague-Dawley rat liver system (Aroclor-induced) in vitro were compared with the binding products of the



primary mouse embryo cell cultures. The DMBA-nucleoside products from mouse skin and mouse embryo cell cultures behave identically upon Sephadex chromatography. Thus, DMBA-DNA binding in mouse skin probably involves 1,2,3,4-ring diol-epoxide, as does the binding to embryo cell DNA. Neither the skin nor the embryo cell products co-chromatographed with the K-region epoxide products. However, when DMBA was activated in the rat system, the hydrocarbon-nucleoside products eluted almost in coincidence with the K-region epoxide marker products. Thus Aroclor-metabolized rat liver microsomes do not mimic the metabolic activation of DMBA in mouse skin or mouse embryo cultures. In both the embryo cell culture and the microsomal system, a metabolite with a retention time of 20 min on high pressure liquid chromatography is the major component. In the microsomal system, a metabolite with a retention time of 16 min is probably the trans-5,6-dihydrodiol. (19 refs)

78-0717 **Effects of Adenosine and Guanosine Cyclic Phosphates and Their Corresponding Nucleosides on Vitamin A-induced Epidermal Tumor Promotion and Growth in Hamster Cheek Pouch.** (Eng) Gaughney, C. (Oral Diseases Res. Lab., Veterans Admin. Sp., Long Beach, CA, 90822); Jensen, J. L.; Stowell, E. *J Med (Basel)* 8(6): 443-456; 1977.

The effects of cyclic AMP (cAMP) and cyclic guanosine 3':5'-monophosphate (cGMP) on 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors in randomly bred female Syrian golden hamsters (LVG:LAK) were determined. Tumors were induced by painting the hamster cheek pouches three times weekly with a 0.2% solution of DMBA for 4 wk. Tumor promotion by vitamin A acetate ( $5 \times 10^{-3}$  M) was tested by painting the pouches with this substance in the presence or absence of the test compounds three times weekly for 6 wk. The animals were then killed and analyzed. Increasing the concentration of cAMP to  $10^{-3}$ - $10^{-5}$  M increased tumor yield and diameter; this partially or completely overcame the net tumor promotion-inhibitory effects occasionally seen with  $10^{-3}$  M cAMP. Increasing the concentration of cGMP to  $10^{-3}$ - $10^{-5}$  M decreased tumor yield with much change in diameter. The relative magnitudes of the increases and decreases varied substantially between experiments at a constant concentration of cyclic nucleotide. AMP demonstrated simultaneous promotion inhibitory and growth stimulatory effects, the former being similar to that of cAMP, tumor yield decreased rather than increased as the concentration of AMP was increased. The opposite result occurred with cAMP. GMP increased tumor yield, similar to concentrations of cGMP, but it did not show the yield-increasing effect of high cGMP concentrations. Adenosine ( $10^{-3}$  M) showed a significant yield-increasing effect similar to that of  $10^{-3}$  M cAMP. Guanosine showed no significant effects at  $10^{-3}$  or  $10^{-5}$  M. (25 refs)

78-0718 **Reproducible Chromosome Changes of Polycyclic Hydrocarbon-induced Rat Leukemia: Incidence and Chromosome Banding Pattern.** (Eng) Sugiyama, T. (Dept. Pathology, Kobe Univ. Sch. Medicine, 7,12-Ikuta-ku, Kobe, Japan 650); Uenaka, H.; Ueda, N.; Fukuhara, S.; Maeda, S. *J Natl Cancer Inst* 60(1): 153-160; 1978.

A study was conducted of 361 leukemias induced in outbred male and female Long-Evans and Sprague Dawley rats by 7,12-dimethylbenz(a)anthracene (DMBA) and 7,8,12-trimethylbenz(a)anthracene (TMBA). Of 345 leukemias in Long-Evans rats, 82 had stemline leukemia cells with #2 trisomy, 10 had cells with long #2 and 220 had normal diploid karyotype. The incidence of #2 abnormalities was 26.7% (DMBA, 31.0%; TMBA, 21.3%). Of 82 trisomy cases, 68 had ordinary #2 trisomy; using DMBA, trisomy was found in 44/150 males and 11/40 females; using TMBA, it occurred in 12/66 males and 15/89 females. The difference between the two chemicals was significant. Of 16 Sprague-Dawley rats, 5 had leukemia with #2 trisomy. Quinacrine fluorescence analysis revealed that cells with #2 trisomy or either of two types of long #2 had total and partial #2 trisomy, respectively. Other chromosome members of cells with long #2, typical #2 trisomy, and "normal diploid" leukemia cells had no band abnormality. Hosts with #2 trisomy leukemia had a significantly lower hematocrit than hosts with normal karyotype leukemias in both DMBA and TMBA groups; this relationship was not noted in leukemias with long #2. These results suggest similar modes of action for both chemicals. (38 refs.)

78-0719 **Cyclic Nucleotides and Their Associated Enzymes in 9,10-Dimethyl-1,2-benzanthracene-induced Mammary Tumors of Rats.** (Eng) Rillema, J. A. (Dept. Physiology, Wayne State Univ. Sch. Medicine, Detroit, MI, 48201); Mulder, J. A.; Anderson, L. D. *Cancer Res* 38(3): 741-744; 1978.

The levels of cyclic AMP (cAMP), cyclic guanosine 3':5'-monophosphate (cGMP), adenylate cyclase, guanylate cyclase, cAMP phosphodiesterase, and cGMP phosphodiesterase were determined in mammary tumors induced in female Sprague-Dawley rats by a single intragastric infusion of 5 mg 7,12-dimethylbenz(a)anthracene and in mammary glands from virgin and midpregnant rats. cAMP levels were higher in tumor tissues than in tissues from midpregnant rats when the data were expressed per mg of protein, RNA, or wet tissue wt; no differences were detected based on DNA content. In tumor vs mammary tissues from virgin rats, cAMP levels were higher in tumor tissues when the results were expressed per mg RNA or wet tissue wt; no differences were observed per mg protein. cGMP levels were lower in tumor tissues than those from virgin or midpregnant rats on the basis of protein and DNA content; no differences were appar-



ent on the basis of mg RNA or wet wt. Adenylate cyclase activities were higher in tumor tissues vs tissues from virgin and midpregnant rats only when expressed per mg RNA or wet wt. Guanylate cyclase activities were less per mg DNA in tumor tissues than in tissues from midpregnant rats; this activity was also less in tumor tissues than in tissues from virgin rats based on protein and RNA content. With a substrate concentration of 10  $\mu$ M, cAMP phosphodiesterase activities in tumor tissues vs those from virgin and midpregnant rats were elevated based on RNA content or wet wt and decreased based on DNA content; with 100  $\mu$ M cAMP, activities were elevated per mg wet wt in tumor tissues vs those from virgin rats and elevated per mg RNA and DNA in tumor tissues vs midpregnant rat mammary glands. With cGMP concentrations of 10  $\mu$ M, activities were elevated per mg RNA and wet wt in tumor tissues vs tissues from virgin and midpregnant rats; with 100  $\mu$ M substrate, activity was elevated per mg wet wt in tumor vs virgin rat mammary tissues. (23 refs)

**78-0720 Relationship Between Insulin and Estrogen Binding to Growth Response in 7,12-Dimethylbenz(a)anthracene-induced Rat Mammary Tumors.** (Eng) Shafie, S. M. (Dept. Biochemistry, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642); Hilf, R. *Cancer Res* 38(3): 759-764; 1978.

The effect of ovariectomy and induction of diabetes (single iv injection of 50-60 mg/kg streptozotocin) on 7,12-dimethylbenz(a)anthracene (DMBA: 5 mg/ml/wk po for 5 wk)-induced mammary tumors in Sprague-Dawley rats was investigated. Tumors that continued to grow after the host was made diabetic (insulin independent) or started to regress after ovariectomy (ovarian dependent) demonstrated decreased insulin binding. Tumors that regressed in diabetic hosts (insulin-dependent) or continued to grow in ovariectomized animals (ovarian-independent) showed an increased insulin-binding capacity. No significant change in insulin binding was observed in tumors that remained static after ovariectomy or induction of diabetes. Insulin-independent tumors demonstrated a significant increase in estrogen binding compared to tumors from intact hosts, and insulin dependent tumors showed decreased estrogen receptor levels. It is concluded that insulin plays a positive role in regulating estrogen-binding capacity, ovarian hormones may play a role in regulating insulin-binding capacity, and that a relationship exists between insulin and ovarian hormones and the growth of DMBA-induced tumors. (26 refs)

**78-0721 The Specificity of the Oestrogen Receptor of DMBA-induced Mammary Tumours of the Rat.** (Eng) Davies, P. (Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Heath Park, Cardiff, CF4 4XX, Wales); Po-

well-Jones, W.; Nicholson, R. I.; Griffiths, K. *Eur J Cancer* 13(12): 1421-1427; 1977.

The specificity of the cytoplasmic estrogen receptor in Sprague-Dawley rat mammary tumors induced by a single dose of 20 mg 7,12-dimethylbenz(a)anthracene (by intubation) was investigated. Apart from compounds containing a phenolic A ring, the most effective compounds were 5-androstene-3 $\beta$ ,17 $\beta$ -diol, 5-androst-3 $\alpha$ ,17 $\beta$ -diol, and 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol. 5-Androstene-3 $\beta$ ,17 $\beta$ -diol appears to compete by binding to the same site as estradiol-17 $\beta$ . Those compounds most effective at diminishing cytoplasmic  $^3$ H-estradiol binding also depressed nuclear  $^3$ H-estradiol-17 $\beta$  binding. The presence of nominal estrogen receptors with a range of affinity for a number of steroids may indicate the presence of a regulatory mechanism superimposed on the basic estrogen controlled system that could be relevant to study of human breast cancer. (26 refs.)

**78-0722 Alternate Fluctuations of Leucine and Thymidine Incorporation by Mammary Tumors in Rats During the Estrous Cycle.** (Eng.) Lee, C. (Dept. Urology, Northwestern Univ. Medical Sch., Ward Memorial Building, 303 E. Chicago Ave., Chicago, IL 60611); Murray, J. J.; Diamond, C. A.; Rafferty, N. S.; Oyasu, R. *Cancer Res* 37(9): 3301-3305; 1977.

Rates of  $^3$ H-leucine and  $^3$ H-thymidine incorporation in 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors were examined during different days of the host's estrous cycle in an effort to associate tumor growth pattern with different synthesis rates in the tumor. Actively growing tumors were surgically removed from 5-day-cycling Sprague-Dawley rats. Tumor pieces were incubated with either  $^3$ H-leucine for 2 hr or  $^3$ H-thymidine for 1 hr. Radioactivity was determined with a liquid scintillation spectrometer. The rate of  $^3$ H-leucine incorporation by the tumors was high at proestrus but dropped significantly to its lowest point the next day, at estrus. During the remaining 3 days of the cycle the rate increased slightly but was still significantly lower than that observed at proestrus. The rate of  $^3$ H-thymidine incorporation was lowest at proestrus and remained low through estrus. The rate began to rise by metestrus, peaked at diestrus 1, and declined by diestrus 2. These rates correlated significantly with tissue mitotic counts. Autoradiographic studies of the tissues collected after incubation with  $^3$ H-thymidine showed that silver grains were localized in the cell nuclei, which supports the incubation condition that  $^3$ H-thymidine has been incorporated into the DNA fraction of the tumor tissue. The results indicate that the growth of DMBA-induced mammary tumors during the estrous cycle is associated with a decrease in  $^3$ H-leucine incorporation at proestrus and a decrease in  $^3$ H-thymidine incorporation during metestrus and diestrus. (21 refs.)



**78-0723 The Cellular Origin of Chemically Induced Tumors.** (Eng) Iannaccone, P. M. (Sir William Dunn Sch. Pathology, Univ. Oxford, South Parks Road, Oxford OX1 3RE, England); Gardner, R. L.; Harris, H. *J Cell Sci* 29: 249-269; 1978.

The cellular origin of chemically induced tumors was investigated in chimeric CBA/HT6T6 mice dimorphic for glucose phosphate isomerase. Several methods of chemical carcinogenesis were used: (1) 0.2 ml of a 0.2% soln of 7,12-dimethylbenz(a)anthracene (DMBA) was applied to the shaved backs of the animals, followed 1 wk later by 0.2 ml of a 0.25% soln of croton oil; the latter procedure was repeated twice weekly until tumors appeared; (2) following DMBA treatment, a 0.005% soln of 12-O-tetradecanoylphorbol-13-acetate (TPA) was applied; (3) 20-methylcholanthrene (20-MC) was applied as a 0.7% soln followed by TPA twice weekly; (4) 2.5 mg 20-MC was injected sc. Four types of tumors were induced: papillomas, squamous cell carcinomas, basal cell carcinomas, and fibrosarcomas. In normal tissue 156/495 samples of epidermis, 398/417 samples of dermis, and 25/25 samples of sc tissue), both a and b types of glucose phosphate isomerase were present. Of 96 tumor samples, however, 46 contained only the a type, 43 only the b type, and 7 both types of the enzyme. An analysis of the size of the clones that formed the chimeric epidermis indicated that the epidermal tumors could not have arisen from more than eight cells. This suggests that the tumors were clonal growths. (4 refs.)

**78-0724 Danazol Therapy in Hormone-sensitive Mammary Carcinoma.** (Eng) Peters, T. G. (Div. Surgery, Medical Coll. Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI 53226); Lewis, J. D.; Wilkinson, E. J.; Fuhrman, T. M. *Cancer* 40(6): 2797-2800; 1977.

The effect of the gonadotropin inhibitor Danazol on dimethylbenz(a)anthracene (DMBA)-induced (20 mg by gavage) hormone-sensitive mammary carcinomas in Sprague-Dawley rats was investigated. Sixty rats in Group 1 received Danazol when the tumor reached 0.5 cm in diameter: 30 received 100 mg/kg/day and 30 received 400 mg/kg/day. Sixty rats in Group 2 received Danazol from the day of DMBA administration; the regimens were the same as those in Group 1. A control group of 30 rats received DMBA only. Adenocarcinomas > 0.5 cm developed in 24/29 controls; 3 of these had spontaneous regression of tumor. Forty-four of 50 surviving rats in Group 1 developed mammary adenocarcinomas. After Danazol treatment, the tumor regressed in 29 and disappeared completely in 15. Danazol resulted in small tumors at 12 wk compared to controls. Seven of 50 Group 2 rats developed mammary adenocarcinomas, and regression occurred in 5. Tumor development was thus inhibited from outset. There was no statistical significance between the

two doses in either treatment group. The response of the glandular epithelium following Danazol was similar to that following oophorectomy. (16 refs.)

**78-0725 A New 7,12-Dimethylbenz[a]anthracene Synthesis: 9-Methoxy- and 10-Methoxy-7,12-dimethylbenz[a]anthracene.** (Eng) Newman, M. S. (Dept. Chemistry, Ohio State Univ., Columbus, OH, 43210); Kumar, S. *J Org Chem* 43(2): 370-371; 1978.

New methods for the synthesis of 9-methoxy-7,12-dimethylbenz(a)anthracene and 10-methoxy-7, 12-dimethylbenz(a)anthracene are presented. The respective syntheses involve the formation of 5-methoxy-3-methyl-3-(2-naphthyl)phthalide and methyl 1-naphthyl ketone, and these compounds are converted into the final compounds. (7 refs)

**78-0726 Detection of Strand Breaks in  $\Phi$ X174 RFI and PM2 DNA Reacted with Ultimate Proximate Carcinogens.** (Eng) Thielmann, H. W. (Institut für Biochemie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany). *Z Krebsforsch* 90(1): 37-69; 1977.

Supercoiled DNA duplexes of phages  $\Phi$ X 174 and PM2 were treated in aqueous solution at neutral pH with ultimate and proximate carcinogens. The carcinogen-treated phage DNA's were then subjected to velocity sedimentation in neutral and alkaline sucrose to quantitate the introduction of single-strand breaks. Reaction of phage DNA with the ultimate carcinogens N-methyl-N-nitrosourea, N-ethyl-N-nitrosourea, 7-bromomethylbenz(a)anthracene, N-acetoxy-2-acetylaminofluorene, and K-region oxides for short periods followed by sedimentation in neutral sucrose gradients led to very few breaks. Incubation with the proximate carcinogens N-hydroxy-2-acetylaminofluorene, 2-acetylaminofluorene, 7-methylbenz(a)anthracene (MBA) and 7,12-dimethylbenz(a)anthracene (DMBA) did not result in breaks. However, when the phage DNA's were reacted with the ultimate carcinogens and then alkali-denatured and sedimented in alkaline sucrose gradients, single-strand breaks were readily introduced. Incubation with the proximate carcinogens followed by alkali denaturation and sedimentation in alkaline sucrose showed that only DMBA and, to a minor extent, MBA caused alkali-inducible breaks. The ability of



N-methyl-N'-nitro-N-nitrosoguanidine to effect the breakdown of superhelical phage DNA in alkali was enhanced in the presence of N-acetylcysteine. (68 refs.)

- 78-0727 **Studies on 3-Methylcholanthrene Induced Leukemia in Mice--3-Methylcholanthrene Administration and Its Effects on Haemopoietic Tissues.** (Eng) Bansal, M. P. (Dept. Biophysics, Panjab Univ., Chandigarh 160014, India); Kalla, N. R.; Kanwar, K. C. *Arch Geschwulstforsch* 47(8): 694-702; 1977.

Biochemical changes accompanying 3-methylcholanthrene (3-MC) induction of leukemia were investigated in ICRC mice. Leukemia was induced by six iv injections of 0.5 mg 3-MC at 7-day intervals. For study of the initial effects, mice were given 1, 2, 3, or 4 0.5-mg doses of 3-MC at 7-day intervals. Leukemia developed in 65% of the animals by approx 3 mo after the first dose. Mice with signs of thymic enlargement were excluded from the biochemical studies. Leukemogenesis was characterized by a fall in RBC counts and fluctuations in WBC counts. A slight initial fall in bone marrow alkaline phosphatase activity was followed by a gradual increase after each administration. Acid phosphatase activity increased in all experimental animals, especially in the spleen. Marrow lactic dehydrogenase activity declined initially, but increased thereafter; in the spleen, however, this activity increased persistently. Acid DNase in the marrow increased significantly only after the first treatment. (27 refs)

- 78-0728 **The Genetic Basis of Susceptibility to Leukemia Induction in Mice by 3-Methylcholanthrene Applied Percutaneously.** (Eng) Duran-Reynals, M. L. (Dept. Pathology, Albert Einstein Coll. Medicine, Bronx, NY, 10461); Lilly, F.; Bosch, A.; Blank, K. J. *J Exp Med* 147(2): 459-469; 1978.

Eight inbred mouse strains carrying the *Ahd* allele [aryl hydrocarbon hydroxylase (AHH)-noninducible] and seven *Ahb* (AHH-inducible) strains were tested for their response to skin painting with 3-methylcholanthrene (3-MC: 1 g/day in 100 benzene for 5 days). 3-MC-painted mice carrying the *Ahb* allele showed a high incidence of papillomas and little or no leukemia. In contrast, mice homozygous for the *Ahd* allele had a high incidence of leukemia and few or no skin tumors. Among mice of a segregating backcross generation that included both *Ahb/Ahd* heterozygotes and *Ahd* homozygotes, skin tumor occurrence correlated directly with AHH inducibility and inversely with the leukemic response. Mice of *Ahd* strains with a high level of endogenous murine leukemia virus (MuLV) expression had a weak skin response without an increase in leukemia incidence. This observation confirms

previous findings that MuLV infection of virus-resistant strains reduces susceptibility to 3-MC tumorigenesis. (17 refs)

- 78-0729 **Chemical Transformation of Human Revertant Cells Induced by Murine Sarcoma Virus.** (Eng) Cho, H. Y. (Microbiological Associates, Bethesda, MD 20016); Arnstein, P.; Rhim, J. S. *Int J Cancer* 21(1): 22-27; 1978.

An attempt was made to transform the human revertant cell line 312H, isolated from nonproducer human osteosarcoma cells (NP/KHOS) induced by Kirsten murine sarcoma virus with 3-methylcholanthrene (MC), 7,12-dimethylbenz(a)anthracene (DMBA), and benzo(a)pyrene (BP). Treatment of the cells for 7 days with various doses of these hydrocarbons indicated that doses of 2.5 µg/DMBA, 50.0 µg/ml MC, and 50.0 µg/ml BP or higher were cytotoxic. Morphologic alterations were noted by the fourth passage in cells treated with 10 µg/ml MC, by the sixth passage with 1 µg/ml MC, by the fifth passage with 1 µg/DMBA, and by the sixth passage with 0.1 µg/ml DMBA. Treatment with 10 or 1 µg/ml BP caused no alteration. Revertant cells transformed by 10 µg/ml MC or 1 µg/DMBA had a six- to sevenfold higher saturation density, larger cell aggregate size, and a higher colony-forming efficiency in soft agar than control and BP-treated (10 µg/ml) cells. Injection of  $5 \times 10^6$  MC- or DMBA-transformed cells into nude mice resulted in poorly differentiated sarcomas at the injection site within 3 wk. Cells treated with 10 µg/BP had no such effect. (12 refs.)

- 78-0730 **Leukemoid Reaction in BALB/c Mice Bearing Primary Tumors Induced by 3-Methylcholanthrene.** (Eng) Kodama, T. (Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 0 Japan); Kawamura, T.; Kobayashi, H. *Cancer Res* 38(3): 715; 1978.

The leukemoid reaction occurring in BALB/cMk, BALB/cMk x C57BL/6 F<sub>1</sub> (CB6F<sub>1</sub>), and C57BL/6 mice bearing primary tumors induced by 3-methylcholanthrene (3-MC) (1.0 mg, sc) and transplanted 3-MC-induced tumors was investigated. In mice bearing primary tumors, fibrosarcomas were noted 63-111 days after carcinogen treatment and death occurred 35-65 days after tumor appearance. A leukemoid reaction was noted in 2/5 BALB/cMk mice and 3/5 CB6F<sub>1</sub> mice 30-38 days after tumor appearance; there was no reaction in C57BL/6 mice. The reaction was similar to that in mice bearing transplanted tumors, but its intensity was low. No tumor metastases were observed. All 13 BALB/cMk and 9 CB6F<sub>1</sub> mice bearing transplanted tumors had leukemoid reactions; in general, the intensity of this reaction was high.



than that in mice with primary tumors. None of the 15 C57BL/6 mice with transplanted tumors had a leukemoid reaction. These findings suggest that host factors, possibly endogenous leukemogenic viruses, are important in the development of a leukemoid reaction. (12 refs)

- 78-0731 **Investigations on the Carcinogenic Burden by Air Pollution in Man. The Effect of a Single Dose of Benzo(a)pyrene in Syrian Golden Hamsters.** (Eng) Ketkar, M. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, 3000 Hannover 61, W. Germany); Reznik, G.; Misfeld, J.; Mohr, U. *Cancer Lett* 3(5/6): 231-235; 1977.

The effect of a single intratracheal dose of 4, 8, or 16 mg benzo(a)pyrene (BP) in either saline or Tris buffer on the respiratory tract of Syrian golden hamsters was investigated. The animals were observed for life or sacrificed when moribund. Respiratory tract tumors were found in 3/30 males and 2/29 females receiving 4 mg BP in NaCl; the corresponding figures for Tris buffer were 5/24 males and 3/27 females. For the 8-mg dose in NaCl, the incidence was 5/28 males and 2/30 females; in Tris, the respective figures were 13/25 males and 2/29 females. For the 16-mg dose in NaCl, the tumor incidence was 4/27 males and 3/23 females; in Tris, the respective figures were 8/27 males and 8/29 females. With the exception of the 4 mg in NaCl group, the difference in male/female incidence was significant. The first tumor in the NaCl group was at 6 wk in the 16-mg group; the first tumor in the Tris group was at 39 wk in the 8 mg group. Laryngeal tumors were either papillomas or squamous cell carcinomas, tracheal tumors were all papillomas, and adenomas and adenocarcinomas were seen in the lungs. However, adenocarcinomas developed in the lungs of the Tris group only, and less-differentiated sarcomas were seen in the NaCl group. The middle and lower segments of the respiratory tract showed hyperplasia, metaplasia, and dysplasia; nasal cavities were free of neoplasms. There were no metastases. (14 refs)

- 78-0732 **New Data on Volcanoes as Natural Sources of Carcinogenic Substances.** (Eng) Ilnitsky, A. P. (Cancer Res. Center, Acad. Medical Sciences USSR, Kashirskoye Shosse, 6, Moscow, USSR); Mischenko, V. S.; Shabad, M. *Cancer Lett* 3(5/6): 227-230; 1977.

A study of benzo(a)pyrene (BP) emission by volcanoes indicated that these emissions vary from volcano to volcano and that degradation in the deposits occurs over time. The BP concentrations in permafrost regions, where degradation is inhibited, were similar to those in areas far from human habitation. (11 refs)

- 78-0733 **Determination of Benzo(a)pyrene in Foods.** (Eng) Saito, Y. (Dept. Foods, Natl. Inst. Hygienic Sciences, 18-1 Kamiyoga 1-chome, Setagaya-ku, Tokyo, Japan); Sekita, H.; Takeda, M.; Uchiyama, M. *J Assoc Off Anal Chem* 61(1): 129-135; 1978.

A four-step procedure for determining benzo(a)pyrene (BP) in foods involves alkali cleavage of the sample, preliminary silica gel column chromatography, selective extraction with concentrated  $H_2SO_4$ , and silica gel column chromatography. Using this procedure, the recovery of BP added to food ranged from 70% to 85%. (12 refs)

- 78-0734 **Contribution of Heat to the Formation of Carcinogenic Hydrocarbons in Food. Part 7. Investigation of Contamination During Smoking.** (Ger) Fritz, W. (Zentralinstitut für Ernährung der Akademie der Wissenschaften der DDR, Bereich Fremdstoffe, Arthur-Scheunert-Allee 114-116, DDR-1505 Potsdam-Rehbrücke, E. Germany). *Arch Geschwulstforsch* 47(8): 685-693; 1977.

Investigations of the benzo(a)pyrene (BP) concentrations in smoked meats revealed that the av level was 0.55  $\mu g/kg$ . Concentrations in meat and sausage smoked industrially differed only slightly from those in foods smoked by a butcher. The BP concentrations in the edible portions of the food were influenced by the ability of the outer casing to retain BP. Av BP concentrations in meats and sausages ranged up to 0.14 using artificial casing, 0.37 using natural gut, and 0.59  $\mu g/kg$  using no casing. This study also indicated that the av BP content in smoked foods (0.36  $\mu g/kg$ ) is considerably lower than that of soft-wood-smoked foods (1.3  $\mu g/kg$ ). BP concentrations in smoked fish were found to be five times higher than those in meats and sausages. The concentration in the skin was particularly high as a result of settling of the smoke components. (25 refs)

- 78-0735 **Benzo[a]pyrene Formation in the Pyrolysis of Selected Amino Acids, Amines, and Maleic Hydrazide.** (Eng) Patterson, J. M. (Dept. Chemistry, Univ. Kentucky, Lexington, KY, 40506); Haidar, N. F.; Smith, W. T.; Benner, J. F.; Burton, H. R.; Burdick, D. *J Agric Food Chem* 26(1): 268-270; 1978.

An isotope dilution-spectrofluorometric method was used to determine benzo[a]pyrene (BP) content in the pyrolyzates of methionine, proline, tryptophan, valine, 2-phenethylamine, N,N-dimethyldodecylamine, and maleic hydrazide. Both pyrodegradation and pyrosynthesis occurred more extensively at 850 C than at 650 C. The respective wts of BP produced at 850 C were as follows (in mg/mole substance pyrolyzed):



2.1, 25, 2.1, 11, 8.0, 57 (with nitrogen as carrier; the wt is 28 with air as carrier), and 11 (with nitrogen as carrier; the wt is 17 with air as carrier). There was no relationship between yield of neutrals and yield of BP at 850 C. Based on these findings, the formation of BP appears to depend more on the structure of the substance pyrolyzed than on the number of carbon atoms in the pyrolyzand. The reason for the different amounts of BP produced with nitrogen and air as carriers is not known. (16 refs)

**78-0736 Correlation of an Electronic Reactivity Index with Carcinogenicity in Polycyclic Aromatic Hydrocarbons.** (Eng) Berger, G. D. (Dept. Chemistry, Yale Univ., New Haven, CT 06520); Smith, I. A.; Seybold, P. G.; Serve, M. P. *Tetrahedron Lett* (3): 231-234; 1978.

The correlation between an electronic reactivity index and the carcinogenicity of polycyclic aromatic hydrocarbons was investigated, with attention being directed to conversion of a dihydrodiol of the parent compound to a dihydrodiol epoxide. With benzo(a)pyrene, formation of the dihydrodiol causes the 9,10 region bond to become highly activated, preparing it for epoxidation. This potential reactivity is represented by a superdelocalizability index. The index was calculated for 25 compounds, and the results were compared with their carcinogenic potencies. Particularly high values were obtained for the carcinogens dibenzo(a,i)pyrene, dibenzo(a,h)pyrene, benzo(a)pyrene, dibenzo(a,l)pyrene, and dibenzo(a,e)pyrene. The degree of accuracy was of the same order of magnitude as the Pullman K and L theory and the alternative bay region carbonium ion approach. It is suggested that the metabolic transformation investigated is important for carcinogenic activity in these compounds. (18 refs.)

**78-0737 Structural Requirements for the Metabolic Activation of Benzo(a)pyrene to Mutagenic Products: Effects of Modifications in the 4,5-, 7,8-, and 9,10-Positions.** (Eng) Wood, A. W. (Dept. Biochemistry and Drug Metabolism, Hoffman-La Roche, Inc., Nutley, NJ 07110); Levin, W.; Lu, A. Y.; Ryan, D.; West, S. B.; Yagi, H.; Mah, H. D.; Jerina, D. M.; Conney, A. H. *Mol Pharmacol* 13(6): 1116-1125; 1977.

The metabolism of benzo(a)pyrene (BP) and eight of its derivatives to products mutagenic to *Salmonella typhimurium* was evaluated in a purified, cytochrome P-448-dependent monooxygenase system free of epoxide hydase. *cis*- and *trans*-BP 7,8-dihydrodiol and 7,8-H<sub>2</sub>BP were activated to the greatest extent, followed by BP and 9,10-H<sub>2</sub>BP. Neither H<sub>4</sub>-7,8-diol nor 7,8,9,10-H<sub>4</sub>BP was metabolically activated to a mutagenic product. Oxidation of the diol groups of BP 7,8-dihydrodiol to form BP 7,8-quinone or saturation of the K-region 4,5-double bond of BP to form 4,5-H<sub>2</sub>BP resulted in mark-

edly decreased metabolic activation. The addition of epoxide hydase to the monooxygenase system almost completely deactivated 9,10-H<sub>2</sub>BP, but it reduced the mutagenicity induced by BP by only 30%. The results emphasize the complex interrelationships of the two microsomal enzyme systems, ie, the cytochrome-dependent monooxygenase and epoxide hydase systems, which are primarily responsible for the metabolic activation and detoxification of BP. (37 refs)

**78-0738 The Interaction of the 7,8-Dihydrodiol-9,10-Epoxy-7,8,9,10-Tetrahydrobenzo(a)pyrene Oxides of Benzo(a)pyrene with Bacteriophage R17 and T7.** (Eng) Shooter, K. V. (Chemical Carcinogenesis Div., Inst. Cancer Res., Royal Cancer Hosp., London SW6 6JB, England); Osborne, M. R.; Harvey, R. G. *Chem Interact* 19(2): 215-223; 1977.

Dose-survival curves were determined for bacteriophage R17 and T7 treated with the syn- and anti-isomers of 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene. 0.02 M phosphate buffer, pH 7.0. In both cases the anti-isomer proved to be the more toxic. The mean lethal dose for R17 was: syn- 3 µg/ml, anti- 2 µg/ml; for T7, the values were: syn- 3 µg/ml, anti- 0.3 µg/ml. With both reagents, reaction with bacteriophage or loss by solvolysis was complete within minutes. Physicochemical studies failed to detect any R17 degradation 1 and 24 hr after the addition of the reagents to the bacteriophage, and no change in bacteriophage survival occurred during this period. In experiments with bacteriophage T7, the diol epoxides did not increase the number of alkali-labile sites in the T7-DNA after 1 hr. These results suggest that no reaction occurs with the phosphate groups of the nucleic acids. Following the initial loss of infectivity when bacteriophage T7 was treated with the syn-isomer, there was a further, progressive loss of biological activity over 4 days, which was associated with the development of alkali-labile lesions. These latter effects were probably due to loss of alkylated bases from the DNA, a process similar to the depurination reactions observed following the reaction of DNA with methylating agents. (20 refs.)

**78-0739 Model Reactions of the Quinone Metabolites of Carcinogenic Hydrocarbons with t-Butylthiol.** (Eng) Beland, F. A. (Ben May Lab., Univ. Chicago, Chicago, IL, 60637); Harvey, R. G. *Bioinorg Chem* 6(4): 419; 1977.

The reaction of benzo[a]pyrene 1,6-dione with t-butylthiol yielded 2-t-butylthio- and 2,4-di-t-butylthiobenzo[a]pyrene 1,6-dione, as determined by nuclear magnetic resonance spectroscopy. An analogous reaction with benzo[a]pyrene 3,6-dione yielded only 12-t-butylthiobenzo[a]pyrene 3,6-dione. These results suggest that in vivo, the quinone metabolites of benzo[a]pyrene and other hydrocarbons may react with nucleophiles such as glutathione and the cysteine component



f proteins to form similar derivatives. Although the glutathione reaction would probably lead only to excretion, the protein-bound quinones from the cysteine reaction could function as catalysts in the production of free radicals. The resulting cellular damage could lead to cancer. (15 refs)

3-0740 **Specificity of Human, Rat and Mouse Skin Epoxide Hydratase Towards K-Region Epoxides of Polycyclic Hydrocarbons.** (Eng) Oesch, F. (Inst. Pharmacology, Univ. Mainz, Obere Zahlbacher Strasse 67, 5500 Mainz, W. Germany); Schmassmann, H.; Bentley, P. *Biochem Pharmacol* 27(1): 17-20; 1978.

Epoxide hydratase (EH) activity was measured in microsomal fractions of skin from male NMRI mice, male Sprague-Dawley rats, and white men and women 28-62 yr of age. In initial experiments, the epidermal and subepidermal fractions were prepared separately, but the specific activity of EH toward benzo(a)pyrene 4,5-oxide as substrate was similar in both layers of human and rat tissue. Whole-skin homogenates were used subsequently. The specific enzyme activities decreased in the order human > mouse > rat. For all three species, the relative activity toward the K-region epoxides of polycyclic hydrocarbons decreased in the order phenanthrene 10-oxide > benz(a)anthracene 5,6-oxide = benzo(a)pyrene 4,5-oxide = 7-methylbenz(a)anthracene 5,6-oxide > 3-methylcholanthrene 11,12-oxide > dibenz(a,h)anthracene 9,10-oxide. The EH activity in human skin microsomal fractions showed little pH dependence, and it was inhibited by low-mol-wt inhibitors in a manner similar to that of the liver microsomal enzyme. The EH activity in the human fractions varied considerably, with values ranging from 175 to 447 nmoles benzo(a)pyrene 4,5-dihydrodiol/min/mg protein. This variation was not due to skin disease, age, or sex, but would have been associated with the area of the body from which the skin was taken. Samples from the abdomen had higher activity than samples from the leg or breast. A comparison with liver values for the three species indicated that pulmonary and hepatic values were essentially similar. (27 refs.)

0741 **Effects of Selenium on Aryl Hydrocarbon Hydroxylase Activity in Cultured Human Lymphocytes.** (Eng) Rasco, M. A. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Center, Houston, TX, 77030); Jacobs, M. M.; Griffin, A. C. *Cancer Lett* 3(5/6):295-301; 1977.

The effects of selenium on the aryl hydrocarbon hydroxylase (AHH) system in cultured human lymphocytes from healthy donors was investigated. The addition of  $10^{-5}$ ,  $10^{-6}$ , and  $10^{-7}$  M Se to the cultures had no effect on cell growth. In cultures of 3-methylcholanthrene-induced or noninduced cells,  $10^{-5}$  M Se had no effect on AHH activity, even when it was present

for the entire culture period. However, when 1, 3, 10, and 100  $\mu$ M benzo(a)pyrene was used as the inducer, 0.1, 0.3, 1, and 10  $\mu$ M Se, respectively, inhibited AHH activity by > 50%. A comparison of AHH inhibition using  $\text{Na}_2\text{SeO}_3$  and  $\text{Na}_2\text{SO}_3$  revealed inhibition by the selenite and no effect by the sulfite. Doubling the concentration of NADPH and NADH (to 2 mM) did not alter these results. (15 refs)

78-0742 **Effects of Harman and Norharman on the Mutagenicity and Binding to DNA of Benzo(a)pyrene Metabolites In Vitro and on Aryl Hydrocarbon Hydroxylase Induction in Cell Culture.** (Eng) Levitt, R. C. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Legraverend, C.; Nebert, D. W.; Pelkonen, O. *Biochem Biophys Res Commun* 79(4): 1167-1175; 1977.

The effects of harman and norharman on the mutagenicity, metabolism, and binding of benzo(a)pyrene (BP) to DNA were investigated in vitro, using liver enzymes from B6 and D2 mice inoculated with 80 mg/kg 3-methylcholanthrene 48 hr before sacrifice, and *Salmonella typhimurium* strain TA98. Both 0.5 mM harman and 1.7 mM norharman inhibited the mutagenicity of BP 50%; differences between preparations from the two strains of mice were not striking. No more than 30% of the bacteria died in any assay, so neither compound is believed to be significantly toxic. Both derivatives also inhibited aryl hydrocarbon hydroxylase (AHH) activity, with the microsomal AHH from D2 mice being approx one order of magnitude more sensitive than that from B6 mice. Both compounds markedly inhibited the binding of total BP metabolites to DNA, and norharman inhibited the formation of all peaks representing specific metabolites bound to one or more nucleosides. At > 0.5  $\mu$ M, both compounds were very toxic to cultures of hepatoma-derived and Hep-1 established cell lines. Concentrations not causing toxicity induced only weak AHH activity in these lines. (30 refs)

78-0743 **Interactions of Norharman and Harman with DNA.** (Eng) Hayashi, K. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo, Japan); Nagao, M.; Sugimura, T. *Nucleic Acids Res* 4(11): 3679-3685; 1977.

The interactions of norharman (9H-pyrido[3,4-b]indole) and harman (1-methyl-9H-pyrido[3,4-b]indole) with DNA were studied. DNA caused remarkable fluorescence quenching and change in the absorption spectra of the dyes. Scatchard plots obtained by optical titration gave Kd values of  $2.2 \times 10^{-5}$  and  $7.7 \times 10^{-6}$  M, and apparent numbers of binding sites of 0.13/base and 0.12/base for norharman and harman, respectively. Agarose gel electrophoresis of circular DNA, closed in the presence or absence of norharman, revealed that the dye inter-



calates DNA, thereby causing  $17 \pm 3$  C unwinding of the double helix. (8 refs.)

- 78-0744 Cutting Fluids and Their Effects on the Skin of Mice: An Experimental Study with Special Reference to Carcinogenicity.** (Eng.) Jepsen, J. R. (Inst. Public Health, Hygiene and Environmental Science, Odense Univ., DK-5000 Odense, Denmark); Stovanov, S.; Unger, M.; Clausen, J.; Christensen, H. E. *Acta Pathol Microbiol Scand [A]* 85(5): 731-738; 1977.

Commercial mineral oil-based cutting fluids caused local and general pathological changes in the skin of mice after repeated topical application. Forty-eight percent of the mice exposed to the oils showed severe dysplasia or malignancy of the skin on histological examination. The corresponding figure for the control group, where various additives were used, was 8%. The frequency of papillomas also increased in the oil-exposed mice. The systemic lesions included focal liver necrosis, associated with amyloid deposition, and amyloidosis of the skin, spleen, and kidneys. The substances responsible for the apparent carcinogenic properties of the cutting oils may be the polycyclic hydrocarbons that are still present after solvent refining. On the other hand, the carcinogens may be the proprietary additives in the cutting oils. (25 refs.)

- 78-0745 Dietary Intake of Nitrate and Nitrite Using the Duplicate-Sampling Portion Technique.** (Eng) Jagerstad, M. (Unit Community Care Sciences, Natl. Board Health and Social Welfare, S-240 10 Dalby, Sweden); Norden, A.; Nilsson, R. *Ambio* 6(5): 276-277; 1977.

The daily dietary intake of nitrite and nitrate by 10 men and 10 women aged 25-60 yr was determined by the duplicate-portion sampling technique. The men and women consumed an av of 66 mg and 70 mg of  $\text{NaNO}_3$ /day, respectively. The nitrite intake was 4.6 mg and 6.6 mg, respectively. These amounts are below the figures set by the World Health Organization (WHO) when calculated in milligrams per day and per kilogram of body wt. Problems of determining the extent of endogenous nitrosamine formation from nitrate and nitrite ingestion are discussed briefly. (20 refs.)

- 78-0746 Occurrence of Nitrate, Nitrite, Dimethylamine, and Dimethylnitrosamine in Some Fermented Nigerian Beverages.** (Eng) Bassir, O. (Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria); Maduagwu, E. N. *J Agric Food Chem* 26(1): 200-203; 1978.

The occurrence of nitrate, nitrite, and dimethylamine in various Nigerian beverages, ie, palm wine, nono (fermented cow's

milk), burukutu (produced from fermented guinea corn), pito (produced from fermented millet), and ogogoro (gin distilled from palm wine), was investigated. These beverages are consumed in fairly large quantities by Nigerians. The three substances were found in all beverages assayed except ogogoro. One sample of palm wine also contained dimethylnitrosamine in hazardous concentrations. These findings underline the health hazard posed by nitrates, nitrites, and secondary amines in food products intended for human consumption. (31 refs)

- 78-0747 Direct or Proximate Contact Between Cells and Metabolic Activation Systems Is Required for Mutagenesis.** (Eng) Kuroki, T. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France); Drevon, C. *Nature* 271(5643): 368-370; 1978.

Mutations in two genetic loci, comprising 8-azaguanine resistance and ouabain resistance were studied in V79 Chinese Hamster cells to determine whether direct or proximate contact between target cells and mediators of metabolism is necessary for the induction of mutagenesis. Mutations were induced by trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (1-2 nanomoles/ml) in cell-mediated mutagenesis systems or N-nitrosodimethylamine (10-30  $\mu\text{moles/ml}$ ) in microsome-mediated mutagenesis systems. In each system, neither mutations nor cytotoxicity was apparent when the cells were separated from the feeder layer or agar mixture by a distance of approx 1 mm. In other experiments, V79 cells were separated from a N-methyl-N'-nitro-N-nitrosoguanidine-containing agar layer by 0.5, 1.0, or 1.5 mm; there was no decrease in cytotoxicity or mutagenicity, compared to unseparated systems. These findings suggest that direct or proximate contact between the target cells and cell membranes or microsome particles, which carry carcinogen-metabolizing enzymes, is essential in cell- and microsome-mediated mutagenesis in mammalian cells. This may also hold for bacterial systems. (12 refs)

- 78-0748 Effect of Dimethylnitrosamine on the Induction of Chromosomal Aberrations in Male Mice and Their F<sub>1</sub> Offspring.** (Eng) Savkovic, N. (Lab. Radiobiology, Inst. Nuclear Science 'Boris Kidric', Belgrade, Yugoslavia); Maric, N.; Pecevski, J.; Radivojevic, D.; Green, S. *Toxicol Lett* 1(4): 179-182; 1978.

The incidence of chromosomal aberrations was investigated in (1) C<sub>3</sub>H male mice treated 5 days/wk for 8 wk with low doses of dimethylnitrosamine (DMN: 0.05 and 0.1 mg/kg) in the tap water and (2) their F<sub>1</sub> progeny. Examination of the testes after treatment and mating revealed no translocations in treated animals or controls. The 56 F<sub>1</sub> progeny had the same results. However, the X/Y chromosome was separated



15 cells of the offspring of 0.05-mg-treated mice and in 38 cells of the offspring of 0.1-mg-treated mice. (23 refs)

8-0749 **The Methylation of DNA in Regenerating Rat Liver.** (Eng) Lawson, T. A. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB 68105). *Krebsforsch* 90(2): 211-214; 1977.

Methylation of liver DNA was studied in male Sprague-Dawley rats given dimethylnitrosamine (DMN: 20 mg/kg ip) alone or in conjunction with partial hepatectomy or 2.5 ml/kg CCl<sub>4</sub> po. There was more persistent methylation if the DMN was given during regeneration following hepatectomy or CCl<sub>4</sub> treatment. DMN metabolism is slowed during regeneration, making the active metabolites available for longer time periods. (12 refs.)

8-0750 **Biochemical Characterisation of Stages of Hepatocarcinogenesis after a Single Dose of Diethylnitrosamine.** (Eng) Pitot, H. C. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 63706); Barsness, J.; Goldsworthy, T.; Kitagawa, T. *Nature* 271(5644): 456-458; 1978.

The development of hepatocarcinomas was studied in three groups of female Sprague-Dawley rats: Group 1 received 0.5% phenobarbital (PB) in their laboratory chow, Group 2 received a single dose of diethylnitrosamine (DEN: 10 mg/kg) 24 hr after partial hepatectomy (PH), and Group 3 was treated with PH + DEN followed 2 mo later by PB. Livers were studied for hepatoma development and the number of enzyme (glucose-6-phosphatase, canalicular ATPase, or  $\gamma$ -glutamyltranspeptidase)-altered foci. Group 1 rats had no hepatomas or altered foci, but Group 3 rats had approx six times the number of altered foci as Group 2 rats. Furthermore, almost all these animals had hepatocellular carcinomas. In Group 2 animals, > 75% of all foci had only single enzyme alteration; however, 45% of the foci in the Group 3 livers exhibited  $\gamma$ -glutamyl transpeptidase, and 30% were equally distributed between those with ATPase deficiency alone and those exhibiting this deficiency in the presence of  $\gamma$ -glutamyl transpeptidase. The relative proportion of foci showing defects of all three enzymes was more than twice that in the Group 2 rats. Thus, two distinct stages of hepatocarcinogenesis exist, and it is possible to identify histochemically the immediate progeny of the putative initiated cells. The mechanism behind the phenotypic heterogeneity of the enzyme deficiency may be related to alterations in messenger RNA template stability. (20 refs)

8-0751  **$\gamma$ -Glutamyltransferase in Putative Premalignant Liver Cell Populations During Hepatocarcinogenesis.** (Eng) Cameron, R. (Dept. Pathology, Univ.

Toronto, Toronto M5G 1L5, Ontario, Canada); Kellen, J.; Kolin, A.; Malkin, A.; Farber, E. *Cancer Res* 38(3): 823-829; 1978.

$\gamma$ -Glutamyltransferase (GGT) activity was measured in different cell populations to determine whether it could be a marker for premalignant hepatocytes. Male Fischer rats were given (1) 2-acetylaminofluorene (2-AAF: 0.02%) in the basal diet for 20 wk; (2) diethylnitrosamine (DEN) at 50 ppm in the drinking water for 36 wk; or (3) a single dose of 100 or 200 mg/kg DEN ip, followed 2 wk later by a basal diet containing 2-AAF, followed 1 wk later by partial hepatectomy; the 2-AAF diet was continued for 1 wk after hepatectomy. Hepatomas induced by 2-AAF or DEN alone had a 30-fold higher GGT activity than in control livers; fetal hepatocytes also had elevated GGT. In animals given DEN, 2-AAF, and surgery, GGT activity was increased in the early putative preneoplastic hepatocytes. By 7 days, the foci had 4 times the activity and by 3 wk, 40 times the activity of control livers. This activity was especially prominent in the bile canaliculi. 2-AAF treatment also induced GGT activity in the proliferating ductal cells, but by 21 days these cells had disappeared, allowing easy identification of the GGT-positive preneoplastic foci. It appears that GGT is a useful marker for preneoplastic hepatocytes. (34 refs)

78-0752 **Carcinogenicity of N-Nitrosodiethylamine in Hibernating and Nonhibernating European Hamsters.** (Eng) Reznik, G. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Reznik-Schuller, H.; Mohr, U. *J Natl Cancer Inst* 58(3): 673-680; 1977.

Hibernating European hamsters reacted differently to sc injection of N-nitrosodiethylamine (DEN) than their nonhibernating counterparts. Hibernating animals tolerated higher dose levels (352-413 mg/kg vs 246-293 mg/kg), but they developed fewer neoplasms. Although hibernating males had more pulmonary tumors than the male nonhibernators, hibernating females given 1/20 of the LD<sub>50</sub> developed fewer lung tumors than nonhibernating females. Survival times were longer for the male hibernators than for male nonhibernators. The organ specificity of DEN, as well as the morphology and histogenesis of the neoplasms, showed no differences between the hibernating and nonhibernating groups. (10 refs.)

78-0753 **Transformation of Tracheal Epithelium Exposed In Vitro to N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG).** (Eng) Steele, V. E. (Cancer and Toxicology Program, Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Marchok, A. C.; Nettesheim, P. *Int J Cancer* 20(2): 234-238; 1977.



An attempt was made to establish cell lines from the tracheal epithelium of 10 to 12-wk-old female Fisher-344 SPF rats after in vitro exposure to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). On days 3 and 6 after the start of culture, explants were exposed for 6 hr to 0.0, 0.001, 1, or 10  $\mu\text{g}/\text{ml}$  of MNNG dissolved in 0.5% dimethyl sulfoxide. All cultures appeared identical for the first 2 to 3 mo, but hyperplastic foci began appearing around days 120-140. The number of primary cultures and the number of subsequently established cell lines was carcinogen dose-dependent. The av number of primary cell cultures obtained after exposures of 0.0, 0.001, 1, 1.0, and 10  $\mu\text{g}$  was 1.3, 1.5, 3.3, and 4.6, respectively. The av yield of cell lines per explant was 0, 0.8, 1.3 and 2.0, respectively. Seven of the 35 established lines produced palpable tumors upon injection into immunosuppressed rats. Five of these lines were from the 10- $\mu\text{g}$  group, two from the 1.0- $\mu\text{g}$  group. The histology of three of these tumors indicated that they were squamous cell carcinomas. This is believed to be the first successful neoplastic transformation of mucociliary epithelium in vitro. (9 refs.)

- 78-0754 **Activation of the Guanylate Cyclase-Guanosine 3'5' Monophosphate System of Colonic Mucosa by N-Methyl-N'-nitro-N-nitrosoguanidine.** (Eng) DeRubertis, F. R. (Dept. Medicine, Veterans Admin. Hosp., Pittsburgh, PA 15240); Craven, P. A. *Cancer* 40(5, Suppl): 2600-2608; 1977.

The effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) on the guanylate cyclase (GC)-guanosine 3'5'-monophosphate (cGMP) system of male Sprague-Dawley rat colonic mucosa were studied. MNNG (1 mM) increased colonic mucosal cGMP from 1.8 to 22.5 picomoles/mg protein in 5 min, and these increases occurred independently of extracellular  $\text{Ca}^{+2}$ . Although 90% of the GC activity in the mucosal homogenates was found in the 100,000-g particulate fraction, the effects of MNNG on mucosal cGMP correlated with the stimulation of 100,000-g soluble GC by this agonist. With 4 mM  $\text{Mn}^{+2}$  as the sole available divalent cation, MNNG increased soluble GC 13-fold over the corresponding basal level; with 4 mM  $\text{Mg}^{+2}$ , the increase was 48-fold. Compared with unstimulated GC, the MNNG-activated soluble enzyme was less dependent upon  $\text{Mn}^{+2}$  availability, and it effectively utilized  $\text{Mg}^{+2}$  as a metal cofactor. N-Ethylmaleimide inhibited the MNNG stimulation of GC and cGMP. Thus, expression of these MNNG actions may involve drug interactions with tissue thiol groups. Prior incubation of MNNG with thiol antioxidants or ascorbate also suppressed the MNNG stimulation of GC, possibly through direct drug reactions involving nucleophilic and electrophilic reactants. It is suggested that a relation exists between the oncogenic properties of MNNG and its ability to activate the colonic mucosal GC-cGMP system. (42 refs.)

- 78-0755 **Early Lesions in Carcinogenesis by N-Ethyl-N'-nitro-N-nitrosoguanidine in Mouse Duodenum.** (Eng) Matsuyama, M. (Lab. Pathology, Aichi Cancer Center Res. Inst., Nagoya, Japan); Nakamura, T.; Suzuki, H.; Ito, M.; Yamada, S.; Nagayo, T. In: *Pathophysiology of Carcinogenesis in Digestive Organs. Proceedings of the 7th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1976*. The Princess Takamatsu Cancer Research Fund (Tokyo, Japan): 441 pp; 269-283; 1977.

N-Ethyl-N'-nitro-N-nitrosoguanidine (ENNG) carcinogenesis in the mouse duodenum was investigated. Preliminary experiments with 50 mg/liter N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the drinking water resulted in leiomyosarcomas only. When ENNG (50 mg/liter) was given to CBA/H-T6 mice for 10 mo, a 44% incidence of duodenal tumors resulted. A second experiment in which 500 or 50 mg/liter ENNG or MNNG were given to mice of several strains for 5 mo revealed a higher incidence of duodenal adenocarcinomas within a shorter period with the higher dose. ENNG gave rise to more duodenal, esophageal, and forestomach carcinomas than MNNG at both doses. A solution of 500 mg/liter ENNG given continuously to Wistar rats for 4 mo induced duodenal adenocarcinomas in 59/62 rats; only 4 gastric adenocarcinomas were induced. The early morphology of ENNG-induced changes was then studied in CBA/H-T6 mice exposed to 500 mg/liter ENNG in the drinking water for up to 20 wk. After 8-10 wk, lateral invaginations of neoplastic cells from the proliferative zone of the crypts were apparent. They consisted of amphophilically stained cells with abnormal mitoses; they proliferated laterally into the lamina propria, where they formed enlarged villi and fused with other villi. These intravillous lesions moved upward and laterally, forming microcrater lesions that invaded the serosa. Enzyme-histochemical analysis of nonneoplastic and neoplastic epithelium in the intravillous, microcrater, and macroscopic lesions showed the cells to be almost identical. No erosion, ulcer, or benign tumor preceded lesion formation. It is suggested that carcinogenesis occurred in one step in the proliferative zone of the crypts. (42 refs.)

- 78-0756 **Effect of Methylnitrosocyanamide on Culture of Mammalian Cells.** (Eng) Ochi, T. (Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho 2-33, Minami-ku, Yokohama 232, Japan); Umeda, M. *Gann* 68(5): 537-542; 1977.

A comparison was made of the biological activities and mutagenicity of methylnitrosocyanamide (MNC) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) on culture of FM3A cells derived from a C3H mouse mammary carcinoma. One-milliliter cell suspensions ( $5 \times 10^4$  cells/ml) containing  $10^{-4}$ - $10^{-6}$  M of each chemical were prepared and after 2 days, the cell numbers were counted by hemocytometer. For the chromosome aberration studies, the



percentage of abnormal metaphases among 100 metaphase was calculated at 6, 24, and 48 hr. In addition, somatic mutation tests were conducted in which the number of guanine-resistant mutations induced by the test compounds was determined. The results of all three experiments showed that MNC was three times more potent than MNNG. Qualitatively, however, their actions were similar. Both MNC and MNNG are unstable at a basic pH, tests were also conducted in Hepes-Hanks buffer solution (pH 7.4), to minimize elevations in pH. The toxicity of MNNG increased in this solution, whereas that of MNC was not. The difference is due to the fact that MNC acts rapidly, within 10 min, but the toxic effect of MNNG increases gradually, up to 120 min. The toxicity of MNC was higher in serum-free medium than in medium containing serum; the toxicity of MNNG was not affected significantly by serum. (21 refs.)

78-0757 **Nitramino Acids. Synthesis and Biological Evaluation of 1-Nitroproline, 1-Nitropipecolic Acid, and N-Nitrosarcosine.** (Eng) Nagasawa, H. T. (Medical Research Labs., Veterans Admin. Hosp., Minneapolis, MN 55417); Muldoon, W. P.; Shiota, F. N. *J Med Chem* 20(12): 1359-1361; 1977.

1-Nitroproline, 1-nitro-DL-pipecolic acid, and N-nitrosarcosine were synthesized from the corresponding nitramino acids and assayed for mutagenic activity. The  $LD_{50}$ 's for the respective compounds were 1.17-1.39, 2.10, and 1.84 millimoles/kg. Assays with *Salmonella typhimurium* indicated that N-nitrosarcosine was marginally mutagenic but that the other two compounds had no mutagenic activity. (25 refs.)

78-0758 **Focal Suppression and Induction of Hyperplasia by the Bladder Carcinogens Butyl(4-hydroxybutyl)nitrosamine and Butyl(3-carboxypropyl)nitrosamine in Organ-cultured Rat Bladder Epithelium.** (Eng) Reese, D. H. (Lung Cancer Branch, NCI, U.S. Public Health Service, U. S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Friedman, R. D.; Gaffney, W.; Keefer, L. K. *J Natl Cancer Inst* 60(1): 219-223; 1977.

The effects of butyl(4-hydroxybutyl)nitrosamine (BBN) and butyl(3-carboxypropyl)nitrosamine (BCPN), its principle primary metabolite, on organ cultures of male Fischer rat bladder epithelium were investigated. Epithelia cultured in medium containing 0.5 and 2.7 millimolar BCPN showed a significant increase in the number of nuclei/unit length of epithelium over controls. The apparent decrease in nuclei/unit length in epithelia cultured in medium containing 2.9 millimolar BBN was not significant. BBN was completely toxic to cells at a concentration of 5.7 millimolar; 5.3 millimolar BCPN

resulted in no apparent loss of epithelial cells. Histograms indicated that epithelia cultured in 0.5 and 2.7 millimolar BCPN had a more heterogeneous population of unit lengths than uncultured epithelia or hyperplastic epithelia cultured without carcinogen. This was also true with 0.6 and 2.9 millimolar BBN. Furthermore, BBN cultures at these concentrations showed higher frequencies of unit lengths with nuclear numbers that were lower than those of controls. With 5.3 millimolar BCPN, many unit lengths of epithelia contained either no nuclei or nuclear numbers well below those of control and uncultured epithelia. The most noticeable and frequent difference between control and carcinogen-treated cultures was a crowding of nuclei in the latter causing the epithelium to appear less differentiated. Areas of epithelia with no signs of carcinogen damage had slight and inconsistent histogram changes. These findings are discussed. (21 refs.)

78-0759 **Experimental Pancreatic Carcinogenesis. II. Lifetime Carcinogenesis Studies in the Outbred Syrian Golden Hamster with N-Nitroso-bis(2-hydroxypropyl)amine.** (Eng) Levitt, M. (Experimental Pathology Branch, Carcinogenesis Res. Program, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD, 20014); Harris, C.; Squire, R.; Wenk, M.; Mollelo, C.; Springer, S. *J Natl Cancer Inst* 60(3): 701-705; 1978.

Male Syrian golden hamsters were treated for life with weekly subcutaneous injections of N-nitroso-bis(2-hydroxypropyl)amine (BHP). The frequency of pancreatic adenomas and carcinomas was as high as 100% (range: 73%-100%), with the first tumors appearing as early as 16 wk. Many of the pancreatic tumors were microscopic, but grossly visible tumors were present in 67% of the animals given 250 mg BHP (in H<sub>2</sub>O/kg body wt), 65% given 125 mg, and 8% given 25 mg. Tumor latency was significantly decreased by the substitution of distilled water for olive oil as the vehicle for the carcinogen. Histologically, the pancreatic neoplasms were ductal adenomas and adenocarcinomas that frequently invaded contiguous structures; ie, the stomach, splenic ligament, mesentery, and serosa of the duodenum and transverse colon. In addition to pancreatic neoplasms, 189/197 hamsters had tumors involving other organs in their gastrointestinal tracts and respiratory systems. In most instances death was attributed to respiratory complications or exsanguination from a ruptured hepatic neoplasm. Marked depletion of splenic lymphoid follicles also occurred in animals dying of single or multiple neoplasms and concurrent pneumonia, suggesting a possible compromise of the immune system. (6 refs)

78-0760 **Evidence for Metabolic  $\alpha$ -Hydroxylation of N-Nitrosopyrrolidine.** (Eng) Hecht, S. S. (Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Pre-



vention, American Health Foundation, Valhalla, NY 10595); Chen, C. B.; Hoffmann, D. *Cancer Res* 38(1): 215-218; 1978.

Evidence was obtained for the metabolic  $\alpha$ -hydroxylation of cyclic nitrosamines, which results in the activation of these compounds to their ultimate carcinogenic forms. Both  $\alpha$ -hydroxynitrosopyrrolidine and 3-formyl-1-propanediazohydroxide, which are unstable intermediates resulting from the  $\alpha$ -hydroxylation of nitrosopyrrolidine, were generated in aqueous solution from the stable precursors  $\alpha$ -acetoxynitrosopyrrolidine and 4-(N-carbethoxy-N-nitrosoamino)butanal. The major product resulting from the decomposition of  $\alpha$ -hydroxynitrosopyrrolidine and 3-formyl-1-propanediazohydroxide was 2-hydroxytetrahydrofuran, the cyclic hemiacetal of 4-hydroxybutyraldehyde. The same product was isolated as its dinitrophenylhydrazine derivative after incubation of rat liver microsomes with nitrosopyrrolidine and after inoculation of rats with nitrosopyrrolidine. These results conclusively demonstrate that  $\alpha$ -hydroxylation is a metabolic process for nitrosopyrrolidine. (27 refs.)

**78-0761 Synthesis of  $\alpha$ -Thio,  $\alpha$ -Sulfinyl, and  $\alpha$ -Sulfonyl-substituted Nitrosamines.** (Eng) Terao, Y. (Shizuoka Coll. Pharmacy, 2-2-1, Oshika, Shizuoka 422, Japan); Matsunaga, K.; Sekiya, M. *Chem Pharm Bull (Tokyo)* 25(11): 2964-2968; 1977.

The synthesis of  $\alpha$ -thio,  $\alpha$ -sulfinyl, and  $\alpha$ -sulfonyl-substituted nitrosamines is described. The reaction comprises nitrosation of alkylaminomethyl alkyl (or aryl) sulfides obtained from primary amine hydrochlorides, formaldehyde, and alkyl (or aryl) thioalcohols. Oxidation of the nitrosamines with metaperiodate and permanganate gives the corresponding sulfoxides and sulfones. (10 refs.)

**78-0762 N-Nitroso-N-methylurea-induced Neurogenic Tumors of the Stomach in Syrian Hamsters.** (Rus) Vasilieva, N. N. (Dept. Carcinogenic Agents, Cancer Res. Center, Moscow, USSR); Milievskaia, I. L. *Arkiv Patol* 39(9): 66-71; 1977.

The carcinogenic effect of relatively small doses of N-nitroso-N-methylurea (NMU) was studied in Syrian hamsters. Animals were subjected to daily injections of NMU into the left cheek pouch (0.1 mg/injection, max dose 7.5 mg over 9 mo). The first tumors started to appear within 31 wk. Of 25 hamsters who survived 31 wk, 20 developed 35 tumors (7 hamsters had multiple tumors). Seventeen of the tumors developed at the application site; in addition, there were tumors of the stomach (11), skin (3), adrenals (1), liver (1), a thecoma of the ovary (1), and one case of reticulosis. Six of the stomach tumors were neurogenic tumors. They were nodular or saucerlike, up to 1.5 cm in diameter, and located in the pylorus. Histologically, these tumors consisted of ganglion cells, Schwann syncytium, and nerve trunk cells. (19 refs.)

**78-0763 Dietary Subacute Toxicity of Ethylene Thiourea in the Laboratory Rat.** (Eng) Freudenthal, R. I. (Battelle Columbus Lab., Columbus, OH 43201); Kerchner, G.; Persing, R. *J Environ Pathol Toxicol* 1(1): 14-161; 1977.

The effects of ethylene thiourea (ETU) on Sprague-Dawley rats were evaluated at concentrations up to 625 ppm in the diet. Only rats fed 125 or 625 ppm ETU demonstrated a toxic response, which was reflected in altered thyroid function. Varying degrees of thyroid microfollicular hyperplasia were noted at levels above 25 ppm, with no effect below this level. (20 refs.)

**78-0764 Mandelonitrile  $\beta$ -Glucuronide: Synthesis and Characterization.** (Eng) Fenselau, C. (Johns Hopkins Univ. Medical Institutions, Baltimore, MD 21205); Pallante, S.; Batzinger, R. P.; Benson, W. R.; Barron, R. A.; Sheinin, E. B.; Maienthal, M. *Science* 198(4317): 625-627; 1977.

The synthesis of mandelonitrile  $\beta$ -glucuronide, patented Laetrile, from rabbit liver uridine diphosphate-glucuronosyl transferase is reported. Positive identification was obtained by thin-layer chromatography, nuclear magnetic resonance, and gas chromatography-mass spectrometry. Several commercial Laetrile preparations were analyzed and found to contain no Laetrile, but amygdalin and an isomer of amygdalin, or amygdalin and neoamygdalin instead. Mandelonitrile  $\beta$ -glucuronide, and amygdalin were tested for mutagenicity against *Salmonella typhimurium* strains TA98 and TA100, and all three compounds were found to be mutagenic. (15 refs.)

**78-0765 Emergency Standard Set for Acrylonitrile.** (Eng) Anonymous (No affiliation given). *Chem Eng News* 56(4): 4; 1978.

The Occupational Safety and Health Administration announced a temporary standard for occupational exposure to acrylonitrile of 2 ppm in air over 8 hr. The previous standard was 20 ppm. This action was prompted by findings of C and ear canal tumors in rats ingesting 35-300 ppm acrylonitrile and an increased incidence of cancer in exposed workers. (no refs.)

**78-0766 A Preliminary Study of Biochemical Changes in the Rat Small Intestine following Long-term Ingestion of Chrysotile Asbestos.** (Eng) Jacobs, R. (Dept. Biochemistry, Univ. Coll., P.O. Box 78, Cathays Park, Cardiff, CF1 1XL, Wales); Dodgson, K. S.; Richards, R. J. *J Exp Pathol* 58(5): 541-548; 1977.



the effect of a 10-mo diet of asbestos and/or food treated with cigarette smoke on the small intestine of 3-mo-old MRC hooded rats was investigated. The rats were fed either an asbestos and cigarette smoke-free diet (1), 0.5 mg asbestos/day (2), 50 mg asbestos/day (3), cigarette smoke-treated food only (4), 0.5 mg asbestos/day treated with cigarette smoke (5), or 50 mg asbestos/day pretreated with cigarette smoke (6). RNA levels in the lumen were significantly lower and DNA levels were significantly higher in all animals receiving asbestos. However, asbestos did not alter the DNA or RNA levels in the mucosa. Only Group 6 had significantly lower protein levels in the lumen. Compared with Group 1, Group 6 had significantly reduced levels of mucosal RNA; this level was also lower than in Groups 2 and 3. Cellular RNA/DNA ratios of Group 4 were lower than in Groups 5 and 6. Group 6 animals had significantly altered ATPase activity in the gut wall. Group 2 animals had significant increases in luminal activities of  $\beta$ -glucuronidase, sucrase, and alkaline phosphatase and mucosal  $\beta$ -glucuronidase compared with Group 1. Group 3 had significant changes in luminal activity of  $\beta$ -acetylglucosaminidase, sucrase, ATPase, and p-nitrophenyl acetate hydrolase compared with Group 1. Groups 5 and 6 had enzymatic change similar to those in Groups 2 and 3. (26 refs.)

78-0767 **The Epidemiology of Cancers of the Upper Alimentary and Upper Respiratory Tracts.** (Eng) Wynder, E. L. (American Health Foundation, New York, NY). In: *Head and Neck Cancer. State of the Art Conference.* February 16, 17 and 18, 1976. (St. Louis, MO: Laryngoscope). Vol. 88, No. 1, Part 2, Suppl. 8, pp. 50-51; 1978.

Cancers of the oral cavity and larynx are rare in nonsmoking and nondrinking populations. Cancer of the larynx is related primarily to cigarette smoking, cancer of the mouth to all types of smoking. Alcohol intake per se does not increase the risk of these cancers, but it potentiates the effect of smoking, probably through associated nutritional deficiencies. (no refs.)

78-0768 **Should Therapeutic Coal-Tar Preparations Be Available Over-the-Counter? (Letter to Editor).** (Eng) Zackheim, H. S. (Redwood City, CA). *Arch Dermatol* 114(1): 125-126; 1978.

Coal-tar preparations for chronic dermatoses are effective, but their uncontrolled use in aqueous solution or in alcoholic solution-type bases can lead to scrotal cancer. Their carcinogenicity (cutaneous and internal) should be evaluated by long-term animal-painting experiments. (6 refs.)

78-0769 **Tumours of Urinary Bladder and Ureter Associated with Abuse of Phenacetin-containing**

**Analgesics.** (Eng) Johansson, S. (Dept. Pathology, Vasa Hosp., S-411 33 Goteborg, Sweden); Wahlqvist, L. *Acta Pathol Microbiol Scand [A]* 85(6): 768-774; 1977.

Clinical and histologic findings are presented for 42 patients (21 men and 21 women) with bladder tumors and 4 patients (2 men and 2 women) with ureteral tumors associated with abuse of phenacetin-containing analgesics. The mean age of the patients was 63 yr; the average total amount of phenacetin ingested, 7.1 kg; the mean exposure time, 21 yr; and the mean induction time, 30 yr. Thirty-four patients had impaired renal function and/or bilateral renal papillary necrosis. In 80% of the bladder tumor patients, recurrent urinary tract infections may have contributed to tumor development. Most tumors were located in the trigone area, close to the ureteral orifices. Twenty-eight patients had low-grade tumors (Grades 1 and 2) and 18 had high-grade tumors (Grades 3 and 4); muscular invasion and metastases were rare. Among the 26 patients who died, uremia due to analgesic nephropathy was the primary cause of death in 14 and a contributory factor in 7. Three of the ureteral tumor patients had received pelvic radiation 15-20 yr prior to tumor diagnosis. (22 refs)

78-0770 **Analgesic Abuse, Renal Parenchymal Disease and Carcinoma of the Kidney or Ureter.** (Eng) Mahony, J. F. (Medical Res. Dept., Sydney Hosp., Sydney, New South Wales, Australia); Storey, B. G.; Ibanez, R. C.; Stewart, J. H. *Aust NZ J Med* 7(5): 463-469; 1977.

The role of analgesics in carcinoma of the kidney and upper urinary tract was investigated in 88 patients with these tumors, 31 of whom had malignant urothelial tumors of the renal pelvis and ureter. Fifteen of these 31 patients had consumed > 5 kg of compound analgesic powders or tablets. In all cases, the analgesic preparations contained aspirin, phenacetin, and (in all but 1) caffeine. Other possible etiological factors include a history of smoking for at least 20 yr (19 patients), long-standing urinary obstruction (7), and transitional cell carcinoma-associated occupation (2); only 4 patients had no identifiable etiological factor. Patients with analgesic nephropathy were characterized by renal functional impairment, hypertension, and interstitial nephritis, but the clinical behavior and pathological appearances of their tumors were similar to those of patients who had not taken analgesics. A metabolite of phenacetin may be the carcinogen involved. (45 refs)

78-0771 **The Administration of Reserpine to Rats for 75 Weeks.** (Eng) Tatamatsu, M. (First Dept. Pathology, Nagoya City Univ., Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Takahashi, M.; Tsuda, H.; Ogiso, T.; Ito, N. *Toxicol Lett* 1(4): 201-205; 1978.

The effect of a 75-wk diet containing 0, 30, or 60 ppm reser-



pine on male and female Wistar rats was investigated. The body wts of male and female rats fed both concentrations of reserpine were significantly lower than those of controls. Histological findings included pituitary adenoma and ovarian cysts in all groups, mammary gland fibroadenomas in the reserpine-treated groups and atrophy of the testis in controls, but no incidences were statistically significant. Significant differences in RBC, WBC, SGOT, SGPT and alkaline phosphatase were found between treated and control groups but not all differences were dose-dependent and histopathological changes could not be correlated with these findings. No association between reserpine dose and breast cancer incidence was noted. (11 refs)

**78-0772 The Feeding of Diets Containing up to 10% Monosodium Glutamate to Beagle Dogs for 2 Years.** (Eng) Owen, G. (Huntingdon Res. Center, Brooklandville, MD, 21022); Cherry, C. P.; Prentice, D. E.; Worden, A. N. *Toxicol Lett* 1(4): 217-219; 1978.

Beagle dogs were fed 2.5%, 5.0%, or 10.0% (wt/wt) monosodium glutamate or 5.13% sodium propionate for 104 wk, and the results were compared with those in control dogs receiving a basal diet. Body wt gain, economy of food consumption, general behavior, electrocardiogram, ophthalmological findings, hematology, blood chemistry, organ wts, and mortality were not affected adversely. Urinary volume and Na excretion were slightly increased in the treated dogs, compared to control dogs, but their ability to concentrate urine was unimpaired. There were no histological differences between treated and control animals. (3 refs)

**78-0773 The Feeding of Diets Containing up to 4% Monosodium Glutamate to Rats for 2 Years.** (Eng) Owen, G. (Huntingdon Res. Center, Brooklandville, MD, 21022); Cherry, C. P.; Prentice, D. E.; Worden, A. N. *Toxicol Lett* 1(4): 221-226; 1978.

Charles River CD rats were fed sodium propionate (2.05% wt/wt) or monosodium glutamate (MSG: 1%, 2%, or 4% wt/wt) for 104 wk, and the effects were investigated. The only significant effect on survival was a better survival rate in females receiving 1% MSG than in untreated female controls. There were no adverse effects on wt gain, hematology, blood chemistry, or organ wts. Water consumption, urinary volume, and Na excretion were increased at 2% sodium propionate and 4% MSG. These increases appeared to be reflected in an increased incidence and early onset of spontaneous subepithelial basophilic deposits in the renal pelvis. Focal mineralization at the renal corticomedullary junction occurred with equal frequency in all rats, including untreated controls. (7 refs)

**78-0774 Long Term Toxicity and Reproduction Study (Including a Teratogenicity Study) with Cyclamate, Saccharin and Cyclohexylamine.** (Eng) Kroes, R. (Natl. Inst. Public Health, P.O. Box 1, Bilthoven, Netherlands); Kroes, R.; Peters, P. W.; Berkvens, J. M.; Verschuuren, H. G.; De Vries, T.; Van Esch, G. J. *Toxicology* 8(3): 285-300; 1977.

Long-term studies of the toxicity, carcinogenicity, embryotoxicity, and teratogenicity of sodium cyclamate, saccharin, and cyclohexylamine in six generations of Swiss SPF outbred mice are reported. Each study included eight experimental groups: control, 5% or 2% sodium cyclamate, 10:1 mixture of 5% sodium cyclamate and 0.5% saccharin, 10:1 mixture of 2% sodium cyclamate and 0.2% saccharin, 0.5% or 0.2% saccharin, and 0.5% cyclohexylamine. Growth retardation, embryotoxicity, a tendency toward delayed ossification, and a decrease in the number of implantations were noted in the cyclohexylamine groups. However, the survival of these animals was better than that of the controls and other treated groups. Tumor incidence was not increased in any group. A total of 7 bladder tumors and 3 cases of bladder calculi were noted in 2,400 animals. It was concluded that neither sodium cyclamate nor saccharin had toxic, embryotoxic or teratogenic effects and that none of the compounds were carcinogenic. (30 refs.)

**78-0775 Saccharin Does Not Bind to DNA of Liver or Bladder in the Rat.** (Eng) Lutz, W. K. (Inst. Toxicology, Federal Inst. Technology, CH-8603, Schwerzenbach, Switzerland); Schlatter, C. *Chem Biol Interact* 19(2): 253-257; 1977.

The binding of saccharin to the liver and bladder DNA of two male Sprague-Dawley rats given 372 or 390 mg/kg saccharin by gavage was investigated. The percentage of saccharin recovered in the first urine fraction was 66% and 84%, total recovery of radioactivity from urine, feces, and cage rinse (animals were killed 50 hr after administration) was 93% and 102%. Radioactivity measurements of DNA isolated from the liver and bladders indicated no incorporation of saccharin. Any binding that does occur is  $< 1$  molecule/ $10^8$  nucleotides in the liver and  $< 1$  molecule/ $10^8$  nucleotides in the bladder. This minimal binding of saccharin is compared to that of N,N-dimethylnitrosamine and benzo(a)pyrene. (16 refs.)

**78-0776 The Topical Effects of Nickel Subsulfide on Renal Parenchyma.** (Eng) Jasmin, G. (Dept. de Pathologie Faculte de Medecine, Universite de Montreal, Montreal, Canada); Solymoss B. *Adv Exp Med Biol* 91: 69-81; 1977.



studies of the carcinogenicity of nickel subsulfide in relation to the site of application are reviewed. In female Sprague-Dawley rats and a Fischer-344 inbred strain, intramuscular injection (10 mg nickel subsulfide in gastrocnemius muscle) produced rhabdomyosarcomas and intrarenal injection (5 mg each pole of the kidney) produced carcinomas that often metastasized to the lungs. When injected iv, the compound produced fibrotic nodules in the lungs but no tumors at this site. One animal developed myeloid leukemia and several developed mammary carcinomas. The renal tumors invaded the renal parenchyma by contiguity and expanded rapidly to the cortical tissue. The early cellular changes involved mainly the distal tubule lining cells with typical inclusions of the nuclei and mitochondria. The animals became plethoric within 1 mo of nickel subsulfide administration, and this phenomenon was associated with erythrocytosis. The possibility that all the observed pathologic alterations resulted from severe disorders in cellular protein synthesis is discussed. (9 refs.)

78-0777 **The Tissue Localization of Nickel Carbonyl in Mice.** (Eng) Tjalve, H. (Dept. Toxicology, Univ. Uppsala, Biomedical Centre, Uppsala, Sweden); Oskarsson, P. *Proc Eur Soc Toxicol* 18: 211-214; 1977.

The distribution of  $^{63}\text{Ni}$ - or  $^{14}\text{C}$ -labeled nickel carbonyl (NC) was investigated in NMRI mice. The mice were given 5  $\mu\text{Ci}$   $^{14}\text{C}$ -labeled NC (13.2 mg/kg) by iv injection or by inhalation. The mice were sacrificed after 5 min and 1, 4, and 24 hr. Additional mice were inoculated iv with 1  $\mu\text{Ci}$   $^{63}\text{Ni}$ -labeled NC (2.6 mg/kg). High radioactivity was observed in the lung parenchyma from 5 min to 24 hr after administration of the  $^{63}\text{Ni}$ -labeled compound. Radioactivity was also seen in the brain, adrenal cortex, heart muscle, adipose tissue, diaphragm, kidneys, and urinary bladder. With the  $^{14}\text{C}$ -labeled compound, most of the radioactivity was found in the blood. When animals that received  $^{63}\text{Ni}$ -labeled NC by inhalation or by iv injection were compared, the former had higher radioactivity in the brain, nasal mucosa, heart muscle, and diaphragm than the latter. Radioactivity in the lungs after 4 days was about 30% of that present at 1 hr. Cellular fractionation of the lungs of  $^{63}\text{Ni}$ -labeled animals at 1 to 24 hr, and 4 days showed that about 50% of the radioactivity was present in the supernatant fraction. The rest was equally distributed among the mitochondrial, microsomal, and nuclei + debris fractions. In the kidney, a higher proportion was present in the supernatant at 1 hr; in the liver, the radioactivity was equally divided among all fractions at all intervals. (5 refs.)

78-0778 **A Comparison of the Effect of Metal Carcinogens Chromium, Cadmium and Nickel on the Interferon System (Letter to Editor).** (Eng) Pribyl, D. (Dept. Toxicology, Univ. San Francisco, San Francisco, CA, 94117); Reagan, L. *Acta Virol (Praha)* 21(6): 507; 1977.

The effect of chromium and cadmium on interferon induction in Newcastle disease virus-treated L-929 fibroblasts was investigated and compared to previous findings with nickel. Unlike nickel, these metals had no definite inhibitory effect, although a reduction in interferon production by cadmium was of borderline significance. Nickel may prevent interferon synthesis rather than release. (4 refs)

78-0779 **Occupational Cancer in Men Exposed to Metals.** (Eng) Houten, L. (Dept. Res. Medicine, Univ. Pennsylvania, Sch. Medicine, Philadelphia, PA); Bross, I. D.; Viadana, E.; Sonnesso, G. *Adv Exp Med Biol* 91: 93-102; 1977.

The incidence of cancer in men occupationally exposed to metals was determined in a survey of Roswell Park patients treated in the period 1956-1965 and representing 21 metal-related occupations. The risk of stomach cancer was elevated in more than half the occupations considered, and the elevation was significant in one-fourth of the occupations. The increased risk was not influenced by workers born in eastern Europe, where the stomach cancer incidence is high, since an American-born subsample also had an elevated risk. However, genetic factors may be involved, and American-born men of eastern European descent may retain old-world dietary habits. No other sites showed more than two significantly elevated occupations: however, six cancers (prostate, lung, bladder, buccal, and kidney) were reported in one-fourth of the occupations considered. Machinists had a significantly elevated risk of leukemia, painters a significantly elevated risk of esophageal cancer. (3 refs.)

78-0780 **Infidelity of DNA Synthesis as Related to Mutagenesis and Carcinogenesis.** (Eng) Loeb, L. A. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111); Sirover, M. A.; Agarwal, S. S. *Adv Exp Med Biol* 91: 103-115; 1977.

Evidence that somatic mutations initiate malignancy and promote tumor progression is summarized. A new screening test for potential mutagens and carcinogens, based on their capacity to decrease the fidelity of in vitro DNA synthesis, is described. In initial studies with 31 metal compounds, all known mutagens and/or carcinogens (Ag, Be, Cd, Co, Cr, Mn, Ni, Pb) decreased the fidelity of DNA synthesis with avian myeloblastosis virus DNA polymerase. Of three metal cations not known to be unequivocal mutagens or carcinogens, only  $\text{Cu}^{2+}$  increased the infidelity of DNA synthesis;  $\text{Fe}^{2+}$  and  $\text{Zn}^{2+}$  did not alter the synthesis. The remaining metals were either presumed noncarcinogens or nonmutagens, and none enhanced the infidelity of DNA synthesis. (32 refs.)

78-0781 **Arsenic Exposure and Mortality: A Case-referent Study from a Swedish Copper Smelter.**



(Eng) Axelson, O. (Dept. Occupational Medicine, Regional Hosp., 701 85 Orebro, Sweden); Dahlgren, E.; Jansson, C. D.; Rehnlund, S. O. *Br J Ind Med* 35(1): 8-15; 1978.

The cause of death was investigated in 251 copper smelter workers (aged 30-74 yr) who died between 1960 and 1976 and 74 controls to determine if there was a relationship between arsenic exposure at the smelter and death due to malignant disease. Lung cancer deaths among workers were increased fivefold over the number expected, and there appeared to be a dose-response relationship between degree of As exposure and the cancer. Most of these cancers were epidermoid and small cell undifferentiated types, but the numbers were too small to permit any conclusions about the distribution. It also appeared that As etching of the skin was associated with lung cancer, and it probably reflected the high intermittent exposure to As. Mortality from leukemia, myeloma, and cirrhosis was also increased slightly. (21 refs)

**78-0782 Measurement of Thyroid Hormone in Experimental Thyroid Tumours in Rats.** (Eng) Al-Hindawi, A. Y. (Inst. Radiology and Nuclear Medicine, Baghdad, Iraq); Black, E. G.; Brewer, D. B.; Griffiths, S. G.; Hoffenberg, R. *J Endocrinol* 75(2): 245-250; 1977.

Thyroid hormone levels were measured in male albino rats fed a diet that supplied a normal amount of iodine. Each rat (except for controls) was given a single ip injection of 25  $\mu$  Ci  $^{131}$ I. One week later, the rats were divided into groups and treated as follows: Group I, no  $^{131}$ I and no other treatment; Group II,  $^{131}$ I only; Group III,  $^{131}$ I and 60  $\mu$ g/ml propylthiouracil (PTU) in the drinking water; Group IV,  $^{131}$ I and 0.5  $\mu$ g/ml L-thyroxine ( $T_4$ ) in the drinking water; and Group V,  $^{131}$ I + PTU +  $T_4$ . There were no tumors in Groups I, II, or IV, and there were no significant difference among these groups with respect to serum concentrations of  $T_4$ , triiodothyronine ( $T_3$ ), or thyroid-stimulating hormone (TSH). However, TSH was significantly higher than normal in Group II at 9 mo and  $T_4$  was higher than normal in Group IV at 3 and 5 mo. All Group III rats developed tumors by 7-9 mo. Serum  $T_4$  and  $T_3$  were low at all times during testing, although free levels rose slightly. Serum TSH was high at all times. Tumor formation in Group V was universal by 9 mo. Both serum and free levels of  $T_4$  and  $T_3$  were normal throughout the study, but TSH was raised significantly at all times. These findings indicate that increased pituitary thyrotrophic drive is a prerequisite for thyroid tumor formation. Irradiation may increase this drive. (10 refs)

**78-0783 Additional Effects of Postpuberal Estrogen Injections on the Vaginal Epithelium in Neonatally Estrogenized Mice.** (Eng) Mori, T. (Zoological Inst., Faculty Science, Univ. Tokyo, Tokyo, Japan); Nishizuka, M. *Acta Anat (Basel)* 100(4): 369-374; 1978.

The effects of high-dose postpubertal estrogen on the genital tract of female C57 black/Tw mice treated neonatally with a low dose of estrogen were investigated. Groups A and B were treated neonatally with 20  $\mu$ g 17 $\beta$ -estradiol in oil the first 3 days of life. Groups A and C were treated at 60 days with 10 sc injections of 100  $\mu$ g 17 $\beta$ -estradiol in oil at 2-wk intervals for 126 days. Groups B and D received only the oil vehicle at this time. All mice were ovariectomized at age 40 days. Group C mice autopsied at 76 or 150 days after the last injection demonstrated atrophy of the vaginal epithelium. Vaginal pieces transplanted from 262-day-old mice to normal ovariectomized hosts showed no changes for at least 30 days. Group A mice had vaginal epithelium that was both stratified and hyperplastic at autopsy performed > 2 months after the last treatment. Vaginal pieces transplanted from 262-day-old mice to normal ovariectomized hosts showed changes for at least 30 days. The vaginal mucosa of Groups B and D mice was normal, and observation of vaginal pieces transplanted from these mice to ovariectomized mice revealed similar atrophic epithelium in both. The uterine epithelium was essentially normal in all mice. (12 refs)

**78-0784 Hyperplastic and Metaplastic Lesions in the Reproductive Tract of Male Rats Induced by Neonatal Treatment with Diethylstilbestrol.** (Eng) Arai, Y. (Dept. Anatomy, Juntendo Univ. Sch. Medicine, Honjo, Tokyo 113, Japan); Suzuki, Y.; Nishizuka, Y. *Virchows Arch [Pathol Anat]* 376(1): 21-28; 1977.

The effect of diethylstilbestrol (DES) on newborn male Wistar rats castrated on the day of birth was determined. Ten mice received 1  $\mu$ g DES for the first 10 days of life, 2  $\mu$ g for the next 10 days, and 4  $\mu$ g for the last 10 days; animals were autopsied at 30, 90 and 270 days. At 30 days metaplastic changes were limited to the ductal portion of coagulating glands (CG) and ejaculatory ducts (ED) adjacent to the urethral opening of the seminal colliculus. By 90 days the lumina of the CG and ED were distended with sloughed cornified cells; epithelial downgrowths were also observed. By 270 days, the lesions were more advanced. The CG and ED were characterized by cellular downgrowths with a pattern of squamous metaplasia without cornification or primary epithelial outgrowths from the urethral wall of the seminal colliculus, resulting in disorganization of the normal transitional epithelial lining. The prostatic utricle developed to an unusual size near the seminal colliculus and was covered by transitional or nonkeratinizing stratified squamous epithelial cells. These changes were not noted in castrated males without DES treatment or intact males. These results indicate that DES induces permanent proliferation of the CG, ED, and dorsal urethral wall near the seminal colliculus. (10 refs.)

**78-0785 Effects of Perinatal Progesterone on Mammary Differentiation In Vitro: Brief Communication.**



lication. (Eng) Warner, M. R. (Meredith Mosle Lab. Can. Res., Dept. Obstetrics and Gynecology, Houston, TX 77030). *J Natl Cancer Inst* 60(2): 465-467; 1978.

The effect of perinatal progesterone (PRG) treatment (100 µg/day for the first 5 days of life) on the in vitro response of C57BL/Crgl mice mammary tissue to mammotropic hormones was investigated. The tissues were grown in culture on wk 4 of life after 4, 6, or 9 days of pretreatment with intraperitoneal injections of 1 mg progesterone and 1 µg of 17β-estradiol. Lobular development was similar in tissues of PRG-treated mice and their controls after in vivo pretreatment. The development was enhanced after 6 but not after 9 days of pretreatment followed by culture with 17β-estradiol, PRG, aldosterone, insulin, and thyroxine. Alveolar development was not enhanced in tissues from PRG-treated mice after 9 days of pretreatment followed by culture with insulin and thyroxine. These results are in contrast to previous findings that perinatal treatment with 17β-estradiol enhances in vitro mammary lobular differentiation in response to exogenous hormones. The events subsequent to neonatal exposure may be necessary to promote the expression of tumorigenic potential in the mammary tissues of mice injected with PRG as neonates. (14 refs.)

78-0786 17β-Estradiol and Enovid Mammary Tumorigenesis in C3H/HeJ Female Mice: Counteraction by Concurrent 2-Bromo-α-ergocryptine. (Eng) Schuch, C. W. (Dept. Anatomy, Michigan State Univ., East Lansing, MI 48824); Adams, C.; Lambrecht, L.; Hassett, C. C.; Brooks, C. L.; *Br J Cancer* 35(3): 328; 1977.

Chronic administration of 17β-estradiol (in drinking water) and the oral contraceptive Enovid (norethynodrel and mestranol: 0.1 mg sc twice weekly) to nulliparous C3H/HeJ female mice, beginning at 1 mo of age and terminating at 20 (17β-estradiol) or 22 mo (Enovid), significantly increased the incidence of mammary tumors over solvent-treated controls. Concurrent treatment of the steroid-treated mice with 2-bromo-α-ergocryptine (CB-154) (0.1 mg/day sc) significantly reduced mammary tumor incidence and primary hyperplastic nodule development to the control level. CB-154 is an efficacious inhibitor of pituitary prolactin secretion. These results demonstrate that steroid-induced mammary gland dysplasias can be sharply reduced by chronic CB-154 treatment, and they suggest that some of the mammary tumorigenic activities of estrogenic steroids in C3H mice are mediated through increased secretion of pituitary prolactin. (32 refs.)

78-0787 Effect of Early Pregnancy on Mammary Tumor Development in Mice (Meeting Abstract). (Eng)

Boot, L. M. (Netherlands Cancer Inst., Amsterdam, Netherlands); Ropcke, G. In: *Fourth Meeting of the European Association For Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 23; 1977. (no refs.)

78-0788 Induction of Estrogen-independent Persistent Vaginal Cornification in Cyproterone Acetate (CA)-induced Feminized Male Mice. (Eng) Suzuki, Y. (Dept. Anatomy, Juntendo Univ. Sch. Medicine, Hongo, Tokyo 113, Japan); Arai, Y. *Anat Embryol* 151(2): 119-125; 1977.

To determine whether feminized male mice could show estrogen-independent persistent vaginal cornification, pregnant ICR/JCL mice were injected with 6 mg of cyproterone acetate (CA) on days 14-20 of pregnancy. The feminized males delivered by cesarean section on day 20 were castrated immediately and treated for the first 10 days of life with injections of 20 or 50 µg estradiol-17β (E<sub>2</sub>). The animals were sacrificed at 60 days of age. All five control animals treated with oil instead of E<sub>2</sub> had atrophic stratified squamous epithelium in the anterior, middle, and posterior parts of the vagina. All nine mice treated with 20 µg E<sub>2</sub> had hypertrophic stratified squamous epithelium (HSSE) in the anterior and middle parts; seven had HSSE in the posterior part also, but in only 2/7 was it cornified. Of 15 mice treated with 50 µg E<sub>2</sub>, 2 had cornified and 13 had noncornified HSSE in the anterior part, 10 had cornified and 5 had noncornified HSSE in the middle, and 13 had cornified and 2 had noncornified HSSE in the posterior part of the vagina. These findings indicate that urogenital sinus epithelial cells could participate in the induction of estrogen-independent persistent vaginal cornification. (20 refs.)

78-0789 Effect of Long-acting Oestriol on the Vaginal Cytology of Postmenopausal Women. (Eng) Purola, E. (Cytology Lab., Dept. Obstetrics and Gynaecology, Univ. Central Hosp., Haartmaninkatu 2, SF-00290 Helsinki 29, Finland); Vartiainen, E. *Ann Chir Gynaecol* 66(4): 216-218; 1977.

The effect of polyestriol phosphate (80 mg, im) on vaginal cytology was determined in eight postmenopausal women. In four patients whose vaginal epithelium showed complete atrophy before treatment, a weak estrogen effect was observed. The effect was noted 1 wk after injection in three patients and 2 wk after injection in one; it lasted 4 wk in three patients and 2 wk in one. Of four patients whose vaginal smears indicated a weak estrogen effect before treatment, no change was noted in three patients and one had a nonsignificant effect. There were no general side effects, local pain, redness, or tissue infiltration. Uterine bleeding was not observed in any patient. (12 refs.)



- 78-0790 The Estrogen-Cancer Controversy.** (Eng) Greenblatt, R. B. (Medical Coll. Georgia, Augusta, GA 30901); Stoddard, L. D. *J Am Geriatric Soc* 26(1): 1-8; 1978.

Although the incidence of endometrial cancer has doubled in the past 25 yr, there is no basis for the assumption that the increase is due to the widespread use of exogenous estrogens. The incidence has also increased in Norway and Czechoslovakia, where estrogens are rarely used. Moreover, incidence statistics may be inflated, as some pathologists tend to diagnose endometrial dysplasias as endometrial cancer. (31 refs.)

- 78-0791 Estrogen Profiles of Premenopausal Women with Breast Cancer.** (Eng) Cole, P. (Dept. Epidemiology, Harvard Sch. Public Health, Boston, MA, 02115); Cramer, D.; Yen, S.; Paffenbarger, R.; MacMahon, B.; Brown, J. *Cancer Res* 38(3): 745-748; 1978.

The value of the estriol ratio (amount of estriol excreted relative to the sum of the amounts of estrone and estradiol) in assessing breast cancer risk was investigated in premenopausal women with breast cancer and in age- and gravidity-matched controls. Despite a lapse of > 2 yr after cessation of oral contraceptive (OC) use, women who had used them for  $\geq 19$  mo had estrogen concentrations lower than those of nonusers. For estrone and estradiol, the reduction was especially marked among the patients, where it averaged 30% compared to 9% for controls. For estriol, however, the reduction was nearly equal for patients and controls. Women who had used OC for < 19 mo generally had estrogen concentrations intermediate to those in the other two groups. For short-term users and nonusers of OC, patients had a higher estrogen concentration and a lower estriol ratio in both the follicular and luteal phases of the menstrual cycle than controls; however, none of the patient-control differences were statistically significant. Patients also had lower levels of pregnanediol excretion than did controls. When patients and controls were compared with respect to other breast cancer risk factors, there was a significant increase in breast cancer incidence with increasing age at first birth (unity = age 24). These findings lend only moderate support to the idea that the estriol ratio or patterns of estrogen metabolism are related to breast cancer risk. (18 refs)

- 78-0792 Exogenous Hormones, Reproductive History, and Breast Cancer.** (Eng) Sartwell, P. E. (Dept. Epidemiology, Johns Hopkins Univ. Sch. Hygiene, 615 N. Wolfe St., Baltimore, MD 21205); Arthes, F. G.; Tonascia, J. A. *J Natl Cancer Inst* 59(6): 1589-1592; 1977.

A study was conducted of 284 breast cancer patients, aged 20-74 yr, and 367 controls to investigate the relationship be-

tween estrogens and oral contraceptives and breast cancer. The age at menarche was nearly identical for both groups. In general, cancer patients had been married at a later age and a larger number (28.1% vs 16.2% of controls) were multiparous. The proportion of cancer patients who had their first pregnancy at  $\geq 20$  yr of age was greater and the mean number of pregnancies was smaller than those for controls, but the differences were not statistically significant. Thirty-four percent of the patients and 23.2% of the controls were premenopausal; 38.4% and 27.5% of the cases had gone through natural and artificial menopause, respectively; figures for the controls were 39.1% and 37.7%. Adjustment was then made for the reproductive factors, and a multiple regression analysis was performed to evaluate the risk prior use of estrogens or oral contraceptives. Although none of the risks differed significantly from unity, the confidence limits on risk for oral contraceptives were large. (14 refs)

- 78-0793 Hematoma of Liver: A Lesion-mimicking Hepatic Neoplasm.** (Eng) Jochimsen, P. (Dept. Surgery, Univ. Iowa Hosps. and Clinics, Iowa City, IA 52242); Platz, C. E.; Pearlman, N. W. *J Surg Oncol* 9: 579-586; 1977.

A 28-yr-old woman with a 91-mo history of oral contraceptive use developed a liver hematoma secondary to hepatic vein thrombosis. It is suggested that the differential diagnosis of a woman with a liver mass and a history of birth control pill use include hepatic vein thrombosis as well as hepatic neoplasm. Inferior venocavography and hepatic venography should be used in these patients to avoid unnecessary exploration. (10 refs.)

- 78-0794 The Association Between Oral Contraceptives and Hepatocellular Adenoma--A Preliminary Report.** (Eng) Rooks, J. B. (Dept. Health, Education, and Welfare, Public Health Service, Center Disease Control, Atlanta, GA 30333); Ory, H. W.; Ishak, K. G.; Strauss, L.; Greenspan, J. R.; Tyler, C. W. *Int J Gynaecol Obstet* 15: 143-144; 1977.

The association between oral contraceptives (OC) and hepatocellular adenoma (HCA) was investigated in 79 women with HCA and matched controls. The risk of HCA in women with 4, 4-7 and  $\geq 8$  yr of OC use was 9, 120, and 500 times higher than the risk in women with < 1 yr of use. Formulations with high hormonal potency were associated with higher risk. Women < 27 yr old, regardless of duration of OC use, had no more than twentyfold increase in HCA risk compared to women of the same age who used no OC preparations < 1 yr. Women  $\geq 27$  yr of age who have used OC  $\geq 7$  yr are at the greatest risk. HCA recurrence in women who continued OC use after tumor removal was 12%. Bleeding tumors were more numerous in women who v



pregnant or postpartum at the time of diagnosis. Bleeding tumors are less likely to occur in women with 1 to 3 yr use than in those with longer use. (4 refs.)

- 78-0795 **Liver Tumors and Oral Contraceptives.** (Eng) Kent, D. R. (Dept. Gynecology and Obstetrics, Univ. California Irvine Medical Center, Irvine, CA 92668); Nissen, E. D.; Nissen, S. E. *Int J Gynaecol Obstet* 15(2): 137-142; 1977.

The association between liver tumors and oral contraceptives (OC) was investigated in 78 women with benign hepatic neoplasia and a history of OC use. Most (> 70%) of the patients were between 20 and 35 yr old; < 1% were < 20 yr old, and 28% were > 36 yr. Exposure to OC ranged from 24 mo to 10 patients to ≥ 60 mo in 42. Although 78% were exposed to at least one product containing mestranol, all combinations were implicated; either conjugated estrogens or progestins alone could produce hepatic changes conducive to tumor development. Sixty of the patients had either focal nodular hyperplasia or hepatic adenoma. Over half had either in or hepatomegaly; the remainder had nonspecific symptoms such as nausea, vomiting, and syncope or they were asymptomatic. Selective celiohepatic angiography is the best method of demonstrating these adenomas. The adenomas are more dangerous when diagnosed during pregnancy. If a tumor has not ruptured, withdrawal of OC will usually result in regression; other methods of treatment are present. It is suggested that a thickening of the media in the small arterioles causes loss of vascular elasticity, neovascular proliferation and thickening of the venous walls. These changes may lead to hypoxia and proliferation of liver tissue. Other methods of pathogenesis and enhancement of rupture are suggested. (11 refs.)

- 78-0796 **Hormonal Regulation of Membrane Phenotype.** (Eng) Carlson, S. A. (Dept. Human Genetics, Univ. Michigan Medical Sch., Ann Arbor, MI 48109); Genter, T. D. *J Supramol Struct* 6(3): 325-331; 1977.

Cultivation of rat hepatoma cells (HTC) in tissue culture with glucocorticoids altered several membrane properties characteristic of transformed cells without affecting the growth rate of these cells. Variant cell lines resistant to dexamethasone inhibition of plasminogen activator production were isolated using an agar-fibrin overlay technique to detect plasminogen activator production by individual colonies of HTC cells. The resistance to dexamethasone was secondary to abnormal or absent glucocorticoid receptors, but due to a lesion in a later step in hormone action specific for plasminogen activator. These variants should prove useful for the study of the mechanism of steroid action as well as for the analysis of the role of proteases in the hormonal regulation of membrane function. (15 refs.)

- 78-0797 **Hepatocarcinogenic Metabolism of Safrole and Its Analogues in Cultured Adult Liver Epithelial Cells (Meeting Abstract).** (Fre) Janiaud, P. (ERA CNRS, Laboratoire de Biochimie Medicale, UER de Medecine 21033 Dijon, France); Delaforge, M.; Morizot, J. P.; Levi, P.; Bonnard, O.; Padieu, P. *Biol Cellulaire* 30(1): 14a; 1977. (no refs.)

- 78-0798 **Long-Term Use of Bromocriptine (Letter to Editor).** (Eng) Thorpe, P. (Sandoz Australia Pty. Ltd., Pharmaceutical Div., P.O. Box 101, North Ryde, New South Wales 2113, Australia); Isaac, P. *Med J Aust* 2(21): 721-722; 1977.

Rats that received bromocriptine for most of their lives developed uterine tumors that appeared to be dose- and time-related. Although equivalent studies in mice were negative and follow-up studies of humans found no evidence of neoplasia, hyperplasia, or metaplasia, regular gynecologic assessment is recommended until the human risks are known. (2 refs.)

- 78-0799 **Malignant Tumors in Rats Fed Nafenopin, a Hepatic Peroxisome Proliferator.** (Eng) Reddy, J. K. (Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL 60611); Rao, M. S. *J Natl Cancer Inst* 59(6): 1645-1650; 1977.

Nafenopin (2-methyl -2- [P-(1,2,3,4- tetrahydro -1-naphthyl)phenoxy] propionic acid), a potent hypolipidemic hepatic peroxisome proliferator, was fed to 15 male F344 rats at a dietary concentration of 0.1% for 25 mo. Between 18 and 25 mo, 11 of the rats developed hepatocellular carcinomas and 1 developed a metastasizing pancreatic acinar cell carcinoma. Two rats with liver tumors also had solitary pancreatic acinar cell adenomas. The hepatocellular carcinomas and the pancreatic acinar cell carcinoma were transplantable successfully through six generations. (19 refs.)

- 78-0800 **Stimulation of Soluble Guanylate Cyclase Activity and Cellular Accumulation of Cyclic Guanosine 3', 5'-Monophosphate by the Carcinogen 4-Nitroquinoline 1-Oxide.** (Eng) DeRubertis, F. R. (Dept. Medicine, Veterans Admin. Hosp., Univ. Pittsburgh, Pittsburgh, PA 15240); Craven, P. A. *J Natl Cancer Inst* 59(6): 1741-1745; 1977.

4-Nitroquinoline 1-oxide (4NQO; 5 milliM) rapidly increased the cellular accumulation of cyclic guanosine 3',5'-monophosphate (cGMP) to peak values 4-13 times higher than basal levels in the liver, lung, renal cortex, and gastric and colon mucosa of rats. This action of 4NQO was expressed



in the presence or absence of extracellular calcium. When added directly to the broken cell preparations, 4NQO also stimulated guanylate cyclase activity three to sixfold over basal levels in the 100,000 x g soluble fractions of each of these tissues. Dicumarol, which blocks the reduction of 4NQO, inhibited 4NQO stimulation of guanylate cyclase and cGMP. Conversely, phenylhydrazine, which enhances the reduction of 4NQO, potentiated the actions of 4NQO on guanylate cyclase and cGMP. These results suggested that the activation of the guanylate cyclase-cGMP system may be mediated by reduction products of 4NQO. The activation of the guanylate cyclase system of 4NQO or its derivatives could function in the expression of carcinogenicity. (37 refs.)

**78-0801 Lower Skin Tumor Incidence in Carcinogen-treated Multiparous Mice.** (Eng) Hoshino, H. (Radiobiology Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan); Tanooka, H. *Cancer Lett* 3(5/6): 285-288; 1977.

Tumor induction in virgin and multiparous JCL-ICR mice was compared. The mice were irradiated with 2.7 kilorads of  $^{90}\text{Sr}$ - $^{90}\text{Y}$   $\beta$  rays and subsequently painted with 0.1 mg of 4-nitroquinoline 1-oxide three times a week for a total of 20 applications. Tumors appeared in the virgins soon after the last application, but tumor formation was slow in the multiparous mice. Although there was no significant difference in the survival patterns of the two groups of mice, the malignant tumor rate in the multiparous mice (1.3%) was significantly lower than that in the virgin mice (12.6%). Papilloma production also appeared to be lower in the multiparous mice. The lower tumor incidence in these mice is presumed to be due to host factors. (5 refs)

**78-0802 Differential Effects of 4-Hydroxyaminoquinoline-1-oxide on Pancreatic and Liver DNA Synthesis in Rats.** (Eng) Denda, A. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara 634, Japan); Inui, S.; Konishi, V. *Chem Biol Interact* 19(2): 225-239; 1977.

The effect of the pancreatic carcinogen 4-hydroxyaminoquinoline 1-oxide (4-HAQO) on DNA synthesis in the rat pancreas and liver was compared. In Wistar rats fed a protein-deficient diet containing 0.5% DL-ethionine for 18 days, pancreatic and hepatic of 500 mg/kg hydroxyurea on day 18 completely inhibited DNA synthesis in both tissues. At 7 mg/kg, iv 4-HAQO inhibited both pancreatic and liver DNA synthesis within 4 hr; however, the inhibition was max (81.5%) in the pancreas, and it lasted for 4 days. Liver DNA synthesis was inhibited to a lesser extent, with DNA values remaining higher than those in rats fed a control diet before 4-HAQO administration. The inhibition of liver DNA synthesis was reversed within 1 day. These results suggest

that 4-HAQO-induced DNA lesions and their repair differ in the pancreas and liver. Pancreatic carcinogens may suppress the ability of the pancreas to respond to mitotic stimuli in the same way that liver carcinogens make hepatic cells unresponsive to mitotic stimuli. This might explain the organotropism of 4-HAQO for the pancreas. (37 refs.)

**78-0803 Comparison of Mutagenicity and Inducibility of DNA Single-Strand Breaks and Chromosomal Aberrations in Cultured Mouse Cells by Potent Mutagens.** (Eng) Tsutsui, T. (Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho 2-33, Minami-Kohoku, Yokohama 232, Japan); Umeda, M.; Maizumi, H.; Saito, T. *Gann* 68(5): 609-617; 1977.

The biological effects of four potent mutagens ethyl methanesulfonate (EMS:  $2 \times 10^{-4}$ ,  $6.3 \times 10^{-4}$ ,  $2 \times 10^{-3}$ ,  $6.3 \times 10^{-3}$  M), N-methyl-N'-nitro-N-nitrosoguanidine (HN<sub>2</sub>:  $10^{-6.5}$ ,  $10^{-6}$ ,  $10^{-5.5}$  M), nitrogen mustard hydrochloride (NH<sub>2</sub>:  $10^{-7}$ ,  $10^{-6.5}$ ,  $10^{-6}$ ,  $10^{-5.5}$  M), or 4-nitroquinoline 1-oxide (4-NQO:  $10^{-7}$ ,  $10^{-6.5}$ ,  $10^{-6}$  M), on cultured FM3A cells from a C3H mouse mammary carcinoma were compared. Treatment with increasing concentrations of each compound increased the mutation frequency in a dose-dependent manner. The ratio of the mutation frequency of the treated cells to that of controls, for the lowest and highest concentrations of each compound, was 1.5 and 44.5 respectively (EMS), 1.5 and 19.2 (MNNG), 2.2 and 100.9 (HN<sub>2</sub>), and 2.2 and 251.9 (4-NQO). Chromosomal aberrations were also induced dose-dependently; a good correlation was shown between the two activities. Mostly chromosomal-type aberrations were observed with EMS, MNNG, and 4-NQO; the chromosome-type was increased considerably with  $10^{-6.5}$  M HN<sub>2</sub>. Alkaline sucrose gradient experiments demonstrated that DNA single-strand breaks were induced only in a high dose range by 1- and 2-hr treatments with the mutagens. One exception was that the 1-hr treatment with HN<sub>2</sub> produced an anomalous sedimentation pattern. These data suggest that caution is necessary in interpreting results obtained by the alkaline sucrose gradient analysis of chemical mutagens with unknown mechanisms of action. Thus, this system for the determination of mutagenicity and chromosomal aberrations is more feasible for screening potential mutagens than analysis of DNA single-strand breaks. (21 refs.)

**78-0804 Ataxia Telangiectasia: The Effects of Chemical Mutagens and X-Rays on Sister Chromatid Exchange in Blood Lymphocytes.** (Eng) Galloway, S. M. (Radiobiology, Univ. California, San Francisco, CA 94143). *Mutat Res* 45(3): 343-349; 1977.

The levels of sister chromatid exchange(s) (SCE) induced by physical (x-rays) and chemical mutagens were studied in



lymphocytes from four ataxia telangiectasia (AT) patients. Lymphocytes from the AT patients and a normal individual were incubated for 3 days in medium containing fetal calf serum and added 25  $\mu$ M 5-bromodeoxyuridine (BUdR) plus  $10^{-7}$  M mitomycin C (MMC),  $3 \times 10^{-4}$  or  $10^{-3}$  M ethyl methanesulfonate (EMS), or  $10^{-7}$  M adriamycin (AM). SCE frequencies were similar in the two groups. When lymphocytes were x-irradiated (50 rads/min at 250 kilovolts), the results were again similar. The effect of 0.4 M 5-bromodeoxyuridine (FUdR) on SCE in normal and AT cells exposed to MMC was also examined. FUdR increased SCE in normal cells, particularly at lower BUdR concentrations. In cells from one AT patient, FUdR appeared to suppress the SCE response, but the reverse effect was seen in her sister. In normal human lymphocytes exposed to x-rays, only slight increase in SCE frequencies were induced after irradiation in this increase was more apparent for cells grown in 0.4  $\mu$ M than in 25  $\mu$ M BUdR. AT cells had a similar response. These findings indicate that the hypersensitivity of AT cells to x-rays and some chemical mutagens is not reflected in an altered ability to produce SCE. (39 refs.)

78-0805

**Evaluation of DNA Repair after MMS Damage In Vivo and In Vitro.** (Eng) Rocci, P. (Istituto di Oncologia, Università di Bologna, 40126-Bologna, Italy); Perocco, P.; Prodi, G. *IRCS Med Sci: Cancer* 5(10): 107-110, 1977.

The DNA repair of Wistar rat spleen and liver cells was investigated in vitro, in vivo-vitro and in vivo after treatment with methylmethanesulfonate (5 or 0.5 mg/ml, 15 mg/100 g body wt iv, and 7.5 mg/100 g body wt iv, respectively). The findings indicated the possibility of detecting in vivo the DNA repair process which takes place in vitro. (3 refs.)

**0806 Pollution by Chemical Mutagens and the Rad-Equivalent System.** (Fre) Latarjet, R. (Institut de Recherches sur le Cancer, 91000 Evry, France). *Entropie* 13(78): 6-11; 1977.

A rad-equivalent system applicable to pollution by chemical mutagens such as vinyl chloride and methyl methane sulfonate is described. The system is based on internationally accepted rules for radiation exposure, and it would permit calculation of the total mutagenic risk of exposure to radiation and chemical mutagens. (11 refs.)

**0807 On the Expressivity of Aberration Hot Spots after Treatment with Mutagens Showing Delayed or Non-delayed Effects.** (Eng) Schubert, I. (Zenit-Institut für Genetik und Kulturpflanzenforschung der DDR, 4325 Gatersleben, E. Germany); Rieger, R. *Mutat Res* 44(3): 337-344; 1977.

The non-random patterns of intrachromosomal distribution of chromatid aberrations induced by agents with delayed effects (ethanol, maleic hydrazide) and agents with nondelayed effects (fast neutrons, x-rays, and bleomycin) were investigated in *Vicia faba*. Nondelayed effects occur when the agent is able to produce aberrations in cells that have completed chromosomal DNA synthesis. Different mutagen concentrations, treatment times, and recovery times did not result in statistically significant differences with respect to patterns of intrachromosomal aberrations. After treatment with nondelayed-effect agents, however, these patterns clearly differed, at least with respect to hot-spot expressivity, from those obtained after treatment with delayed-effect agents. These differences were probably due to the different modes of action of these two groups of agents. The induction of chromatid aberrations by mutagens with delayed effects was confined to the DNA replication period(s) of interphase, suggesting that most of the DNA double-strand breaks arise by gap formation opposite a primary lesion in the template strand during DNA replication. The nondelayed-effect agents induced base damage, single-strand scissions, and probably double-strand breaks in the DNA immediately and, therefore, were able to induce chromatid aberrations during the  $G_2$  phase of the cell cycle, when DNA replication is completed. (35 refs.)

**78-0808 Types of Chromosome Aberrations after Combined Exposure to Various Chemical Mutagens.** (Rus) Nazarenko, S. A. (Lab. Mutagenesis, Inst. Medical Genetics, Moscow, USSR). *Biull Eksp Biol Med* 85(1): 79-81; 1978.

The cytogenic effect of combined exposure to various concentrations of thiophosphamide and dipine was studied in cultured human peripheral blood lymphocytes. The tested concentrations ranged from  $3.17 \times 10^{-5}$  M to  $22.19 \times 10^{-5}$  M. Both mutagens affected the  $G_0$  phase, but the yield of single breaks and the number of chromatid exchanges after exposure to thiophosphamide was almost twice those obtained after exposure to an equimolar concentration of dipine. Combined exposure to both mutagens did not enhance the yield of aberrations, which indicated the additive effect of the tested agents. (9 refs.)

**78-0809 Cytochrome P-450 and the Activation of Promutagens in *Saccharomyces cerevisiae*.** (Eng) Callen, D. F. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709); Philpot, R. M. *Mutat Res* 45(3): 309-324; 1977.

The ability of the cytochrome P-450 of *Saccharomyces cerevisiae* to activate promutagens was investigated. Two diploid strains of *S. cerevisiae* were used: D4, which is heteroallelic at the *trp5* and *ade2* loci, and D5, which contains *ade2-119* and *ade2-40* at the *ade2* locus. When D5 was grown with 2%,



4%, 6%, or 10% glucose as the sole carbon source, the glucose concentrations of cytochrome P-450 per gram of dry wt reached a max at approx 10 hr and then decreased; cytochrome oxidase was not detectable at the P-450 max. The variation of cytochrome P-450 and cytochrome oxidase in strain D4 grown in 2% glucose was similar to that of D5. There was no detectable cytochrome P-450 in whole-cell suspensions from D4 or D5 grown with 2% galactose as the sole carbon source. D4 cells were then grown in 2% glucose and treated with varying concentrations of aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), dimethylnitrosamine (DMN), ethyl carbamate,  $\beta$ -naphthylamine, cyclophosphamide, or dimethyl sulfoxide. For all compounds except AFB<sub>1</sub>, there was a narrow concentration range at which genetic activity could be observed, and a small increase in dose resulted in a rapid decrease in survival. The *trp5* locus was always a more sensitive indicator of genetic damage than *ade2*. D4 cells isolated from medium containing galactose had approx 10 times less cytochrome P-450 than cells from a glucose medium, and for all compounds except AFB<sub>1</sub>, there were only marginal conversions above control values. With AFB<sub>1</sub>, the response was only slightly less than that with glucose-grown cultures. D5 cells grown on galactose were treated with AFB<sub>1</sub> and DMN. These cells were not as indicative of genetic damage as D4 cells. Furthermore, D5 was more sensitive than D4 to AFB<sub>1</sub> but less sensitive than D4 to DMN. (28 refs.)

- 78-0810 **Carcinogen Activation by Human Liver Enzymes in the Ames Mutagenicity Test.** (Eng) Tang, T. (Dept. Microbiology, Virginia Commonwealth Univ., Richmond, VA 23298); Friedman, M. A. *Mutat Res* 46(6): 387-394; 1977.

The ability of human liver post-mitochondrial supernatants from 10 individuals (7 males, 3 females: aged 3 days to 92 yr) to activate benzidine, 2-aminobiphenyl, 4-nitrobiphenyl, 3,4-benzo(a)pyrene (BP), 2-naphthylamine, sterigmatocystin, 3-methylcholanthrene (3-MC), 2-acetylaminofluorene (2-AAF) and aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) in the Ames mutagenicity test with *Salmonella typhimurium* TA 100 was studied. All compounds were tested at 10, 50, and 500  $\mu$ g/plate except AFB<sub>1</sub> and sterigmatocystin, which were tested at 0.1, 1, 5, 25, and 50  $\mu$ g/plate. The activation ability of the samples ranged from undetectable to highly active for 2-AAF. None of the samples activated benzidine. Low activation activity was observed for 3-MC and BP; most samples were positive for activation of 4-nitrobiphenyl. The highest mutagenic activity was observed for AFB<sub>1</sub> and sterigmatocystin. Thus human enzyme systems, like those of rodents, are more effective in inducing mutagenic activity from mycotoxins than aromatic amines and polynuclear aromatic hydrocarbons. The varia-

tion in activation ability of the different human samples difficult to interpret because of the large age range and the fact that five of the patients had cancer and were generally treated with some form of chemotherapy. (14 refs.)

- 78-0811 **OSHA on the Move.** (Eng) Embler, L. (No affiliation given). *Environ Sci Technol* 11(11): 1142-1147; 1977.

Problems confronting the Occupational Safety and Health Administration (OSHA) in the regulation of industrial chemicals are discussed. A four-category Cancer policy system is proposed, with category I representing confirmed carcinogens; II, suspect carcinogens; III, compounds for which there is insufficient evidence to classify them higher; IV, substances not found in US industries. It is estimated that the 2,000 chemicals listed by the National Institute for Occupational Safety and Health as suspect carcinogens and currently used industrially, 200 are in I and 300-400 are in II. The remainder are in III and IV. (no refs.)

- 78-0812 **Hamster-Embryo-Cell Transformation In Vitro (Meeting Abstract).** (Eng) Clynes, M. M. (Dept. Zoology, Univ. Coll., Belfield, Dublin 4 053 Ireland); Duggan, E. J. *Biochem Soc Trans* 5(6): 1731-1732; 1977. (17 refs.)

See also:

- \* (Rev.): 78-0601, 78-0602, 78-0603, 78-0604, 78-0605, 78-0606, 78-0607, 78-0608, 78-0609, 78-0610, 78-0611, 78-0612, 78-0613, 78-0614, 78-0615, 78-0616, 78-0617, 78-0618, 78-0619, 78-0620, 78-0621, 78-0622, 78-0623, 78-0624, 78-0625, 78-0626, 78-0627, 78-0628, 78-0629, 78-0630, 78-0631, 78-0632, 78-0633, 78-0634, 78-0635, 78-0636, 78-0637, 78-0654, 78-0664, 78-0666, 78-0667, 78-0670.
- \* (Phys.): 78-0824, 78-0825, 78-0831, 78-0836.
- \* (Viral): 78-0845, 78-0866, 78-0880, 78-0881, 78-0890, 78-0910, 78-0929.
- \* (Immun.): 78-0942, 78-0944, 78-0945, 78-0946.
- \* (Path.): 78-1024, 78-1026, 78-1041, 78-1042, 78-1044, 78-1050, 78-1055.
- \* (Epid.-Biom.): 78-1117, 78-1119, 78-1120, 78-1121, 78-1122, 78-1126, 78-1127, 78-1128, 78-1129, 78-1130, 78-1131, 78-1132, 78-1133, 78-1134, 78-1136, 78-1137, 78-1138.



## PHYSICAL CARCINOGENESIS

78-0813 **Widespread Dermal Infiltration and Dermal Cytology of Osteogenic Sarcoma.** (Jpn) Kimura, K. (Kyoto Second Red Cross Hosp., Kyoto, Japan); Yamashita, W.; Sato, M. *Acta Dermatol Kyoto (Engl Ed)* 2(3/4): 121-128; 1977.

A 76-yr-old woman had an osteogenic sarcoma of the left humerus with continuous and diffuse dermal infiltration via the surrounding soft tissue. Seventeen years previously, she had undergone left mastectomy and irradiation for breast carcinoma. Her previous treatment may have played an etiological role in sarcoma development. Dermal cytology was useful in the diagnosis. (18 refs)

78-0814 **Second Malignancies Following Radiotherapy of the Vocal Cord - Radiation-induced Cancer?** (Ger) Herrmann, I. F. (Wurzburg, W. Germany); Gay, C. *Arch Otorhinolaryngol (NY)* 216(2): 562-564; 1977.

A total of 887 patients treated with radium, <sup>60</sup>Co, or ultrashort rays for cancer of the vocal cord between 1953 and 1974 were examined for radiation-induced second malignancies. There was no way of determining if the second cancers were caused by the surviving tumor cells or by iatrogenic means. Most patients with second tumors had a history of smoking or exposure to other carcinogens. It was thus not possible to determine conclusively if radiation induced the second malignancy. (no refs.)

78-0815 **Breast Cancer Following Irradiation of the Breast.** (Eng) Baral, E. (Radiumhemmet, Karolinska Hosp., S-104 01 Stockholm 60, Sweden); Larsson, L.; Mattsson, B. *Cancer* 40(6): 2905-2910; 1977.

The incidence of breast cancer was determined in 1,037 women irradiated between 1927 and 1957 for nonmalignant conditions of the breast: fibroadenomatosis (855), acute mastitis (20), chronic mastitis (49), and unilateral breast hypertrophy (13). To decrease the influence of subclinical cancers on the calculations, 14 cancers that were diagnosed within 5 yr of treatment were excluded. Follow-up of the 1,023 remaining patients averaged 31.5 yr. Of these, 115 had cancers in the irradiated breast, 20 in the nonirradiated breast. Based on 1970 cancer incidence figures, only 48.6 tumors were expected; the difference is highly significant. Patients whose treatments spanned  $\leq 60$  mo had a cancer incidence of 9%, while those treated  $> 60$  mo had an incidence of 37%. The

estimated median radiation dose for 12 mo of treatment was 580 rads when cancer developed and 550 rads when it did not; for 12-60 mo of treatment, the respective doses were 1,810 and 1,580 rads; for  $> 60$  mo, the respective doses were 2,000 and 1,770 rads. Based on patients whose treatment was  $< 12$  mo, there was a higher risk of cancer when the breasts were irradiated at lower ages. With radiation doses of 1-499 rads, 500-999 rads, and 1,000-1,499 rads, the respective latent periods were 25, 26, and 24 yr. With doses of 1,500-3,999 rads, there was a 20-yr latent period. Thus, irradiation of the breast for nonmalignant conditions increases the incidence of breast cancer. (24 refs.)

78-0816 **Thyroid and Breast Cancer Following Childhood Radiation.** (Eng) Curtin, C. T. (Dept. Pathology, Riverview Hosp., Red Bank, NJ 07701); McHeffey, B.; Kolarsick, A. J. *Cancer* 40(6): 2911-2913; 1977.

One year after excision of benign and malignant (follicular carcinoma) thyroid lesions in a 35-yr-old man, he underwent left radical mastectomy for infiltrating duct carcinoma of the breast. At the age of 6 mo, he had received seven weekly radiation treatments to the mediastinum for status lymphaticus. Because of the patient's age and radiation history, an association between the cancers and radiation is suggested. (16 refs.)

78-0817 **Leukemia in Children of Mothers with Carcinoma of the Thyroid Following Irradiation of the Thymus as Children (Letter to Editor).** (Eng) Hurvitz, C. H. (Div. Pediatric Oncology and Immunology, Dept. Pediatrics, Cedars-Sinai Medical Center, 87 Beverly Blvd., Los Angeles, CA 90048); Gatti, R. *J Pediatr* 91(6): 1023-1024; 1977.

The occurrence of leukemia in children of mothers with carcinoma of the thyroid and a history of thymic irradiation as children is discussed based on two cases. A 6-yr-old boy developed acute lymphocytic leukemia 7.5 yr after thyroid carcinoma had been diagnosed in his mother. She had undergone thyroidectomy during pregnancy and had received radioactive iodine after delivery, but had refrained from contact with the child for 4 days. At 5 yr of age, she had received radiation to the chest for asthma. Acute lymphocytic leukemia developed in the 3-yr-old daughter of a woman who was diagnosed as having thyroid cancer when the child was 15 mo old. At the age of 10 mo, the mother had received two doses of radiation for breathing difficulty. (5 refs.)



- 78-0818 Tumor Development as a Delayed Effect of X-Ray Therapy of the Head and Neck.** (Ger) Schaupp, H. (Frankfurt, W. Germany); Rosemann, G. *Arch Otorhinolaryngol* (NY) 216(2): 560-561; 1977.

As a result of a study of 18 radiogenic tumors of the head and neck, including 3 sarcomas that developed following irradiation for retinoblastoma, recommendations for radiation therapy are presented. X-ray therapy should only be used for malignant conditions, basal cell carcinomas should be excised when possible and not irradiated, and there should be limited use of radiotherapy in young patients with totally excised small tumors and no malignancy in the regional lymphatics. (no refs.)

- 78-0819 Premature Chromosome Condensation in Persons Exposed to Occupational Radiation and in Tumour Patients Receiving Therapeutic Radiation.** (Eng) Anger, H. (Abteilung für Medizinische Genetik der Nervenklinik, Charité, Schumannstrasse 20/21, DDR-104 Berlin, E. Germany); Witkowski, R. *Radiobiol Radiother (Berl)* 18(5): 633-638; 1977.

Peripheral blood lymphocytes from persons exposed to occupational radiation and from cancer patients receiving therapeutic radiation were studied for the occurrence of premature chromosome condensation (PCC). A total of 154 persons formed nine groups as follows: (1) 20 women, 14 men with chronic whole-body radiation of < 5 rem/yr; (2) 7 women, 20 men with Group 1 exposure plus partial-body radiation of 1.5 to 2,200 rads; (3) 11 women, 25 men with Group 1 exposure plus acute whole-body irradiation of 200 millirads-52 rads; (4) 33 men with up to 15 yr exposure to ionizing radiation, 3 with additional exposure to arsenic; (5) 2 men who had received Thorotrast 30 yr previously; (6) 5 women, 6 men treated with 600 to 15,200 rads fractionated radiation for cancer; (7) 5 men treated with  $^{60}\text{Co}$   $\gamma$ -radiation for esophageal cancer; (8) 4 women, 4 men who received up to 1,200 rads of fast neutrons; and (9) 13 women, 8 men who served as controls. The number of cells with PCC were as follows: Group 2, 0.22%; Group 3, 0.16%; Group 4, 0.16%; Group 5, 1.33%; Group 6, 0.18%; Group 8, 0.42%. In addition, the number of structural chromosome, chromatid, and numerical aberrations were increased in the irradiated persons. (24 refs.)

- 78-0820 Effects of Fast Neutron Irradiation on the Development of the Mouse Brain.** (Eng) Deguchi, H. (Dept. Anatomy, Hiroshima Univ. Sch. Medicine, Hiroshima, Japan). *Hiroshima J Med Sci* 26(2/3): 127-147; 1977.

The effects of fast-neutron irradiation on the development of the mouse brain were investigated. On the 4th to 11th days

of pregnancy, mice were irradiated with 14.1 megavolts of fast-neutron radiation at a dose of 100 rads, and the fetuses were examined macroscopically and histologically on the 4th to 19th days of gestation. Sixty-one of 73 externally malformed fetuses were examined. Two cases of exencephaly were seen in fetuses irradiated on day 7, 2 cases of microcephaly in those irradiated on day 9, and 2 cases of hydrocephalus in fetuses irradiated on day 6, 3 cases in fetuses irradiated on day 11. Four tumors were observed: three in fetuses irradiated on day 7 of pregnancy and one following irradiation on day 10. The tumors consisted of homogeneous ventricular cells without any sign of malignancy. Three to 4 days after irradiation on day 10 or 11 of pregnancy, rosette formation was observed in the pallium, but the rosettes began to disappear within a few days. The results suggest that slight damage to brain tissue by fast-neutron irradiation can be repaired without resulting in any external morphological abnormalities. It is possible that not only neuroblasts, but also the fibroblast-like cells that invade the brain at times during the fetal period are involved in the repair. (63 refs.)

- 78-0821 Chromosome Aberrations in Normal Leukocytes Induced by the Plasma of Exposed Individuals.** (Eng) Pant, G. S. (Dept. Radiology, All India Institute of Medical Science, Ansari Nagar, New Delhi 110016, India); Kamada, N. *Hiroshima J Med Sci* 26(2/3): 149-154; 1977.

A study was undertaken to determine whether a chromosomal breaking factor (CBF) exists in the plasma of atomic bomb survivors, and, if it does, whether the frequency and types of chromosomal breaks are the same as those seen in patients who were x-irradiated for cancer treatment. The WBC of normal individuals were cultured with autologous plasma (controls), plasma of patients who had received large doses of radiation for the treatment of malignant tumors, and plasma of heavily exposed atomic bomb survivors. An average 3.7% chromosomal breaks was observed in 600 metaphases from control cultures, 12.5% in 839 metaphases from plasma cultures of x-irradiated patients, and 10.9% in 1,438 metaphases from plasma cultures of atomic bomb survivors. The aberrations were mostly of the chromatid type; other types included isochromatid breaks, acentric fragments, deleted chromosomes, and translocations/inversions. There were significant differences, in either the frequency or type of chromosome aberrations, between the plasma from the irradiated individuals and that from the atomic bomb survivors. These results indicate that a CBF exists in the plasma of irradiated individuals and that it circulates in the bloodstream up to 31 yr after radiation exposure. (29 refs.)

- 78-0822 On "Conservative" Estimates of Radiation Hazards.** (Eng) Swartz, H. M. (Dept. Radiology, Medical Coll. Wisconsin, Milwaukee County Medical



plex, Milwaukee, WI 53226). *Radiology* 126(1): 267-268; 1983.

The problem of extrapolating from high to low doses in assessing radiation hazards is discussed in terms of mammographic screening of women for cancer. It is concluded that a conservative risk/benefit ratio cannot be established because it is not known which carries a greater risk: mammography or discontinuation of its use. (4 refs.)

78-0823 **US Soldiers in Cancer Study.** (Eng) Dickson, D. (No affiliation given). *Nature* 271(5644): 399; 1978.

The US Department of Defense is investigating the carcinogenic effects of radiation in 2,235 soldiers who took part in maneuvers following the detonation of a nuclear device in Nevada in 1957. The eight reported cases of leukemia in this group have been declared out of the normal range. The threshold hypothesis for radiation is criticized. (no refs)

78-0824 **Enhancement of DMBA Tumorigenesis in Hamster Cheek Pouch Epithelium by Repeated Exposures to Low-Level X Radiation.** (Eng) Lurie, A. G. (Connecticut Health Center, Dept. Oral Radiology, Farmington, CT 06032). *Radiat Res* 72(3): 499-511; 1977.

The effects of repeated exposures to low-level x-radiation on the incidence, volume, and latent period of 7,12-dimethylbenz(a)anthracene (DMBA)-induced neoplasms were examined in Syrian hamster cheek pouch epithelium. Doses were 0.05 ml of 0.1% DMBA in mineral oil twice weekly for 10 wk and 20 R head and neck x-irradiation once weekly for 17 wk. Animals received either radiation alone, DMBA alone, or simultaneous radiation + DMBA. Radiation alone did not result in any detectable pathology changes. Incidence (68% vs 40%) and volumes of tumors (7.64 vs 0.69 mm<sup>3</sup>) were significantly greater in animals receiving radiation + DMBA than in animals receiving DMBA alone. Latent period for earliest tumor appearance was shorter in animals receiving radiation + DMBA than in animals receiving DMBA alone (9 vs 24 wk). The results are compatible with low-level x-radiation acting either as a synergistic carcinogen or as a tumor promoting agent. (43 refs.)

78-0825 **Effect of Radioprotective Amino Thiols on the Induction and Repair of Single-Strand Breaks in the DNA of Irradiated Mammalian Cells.** (Eng) Modig, G. (Radiation Biology Unit, Dept. Tumor Biology, Karolinska Institutet, S-104 01, Stockholm, Sweden); Edgren, M.; Olsson, L. *Acta Radiol [Ther]* (Stockh) 16(3): 245-256; 1977.

The in vitro effect of two thiols, cysteamine (CA) and 2-mercaptopropionylglycine (MPG), on the induction and repair of single-strand breaks in the DNA of V-79 Chinese hamster cells was investigated. The breaks were produced by irradiation in the presence or absence of O<sub>2</sub>. In preliminary experiments, CA and MPG were found to be toxic, increasing the degradation of DNA in unirradiated cells with increasing concentration and incubation time. Therefore, thiol concentrations ≤ 20 mM and incubations ≤ 25 min were used. The cells were exposed to 39 Gray units (Gy, 3.44 Gy/min) of radiation 10 or 25 min after the addition of 5, 10, or 20 mM CA or MPG to the medium. In the presence of O<sub>2</sub>, both CA and MPG reduced the initial yield of single-strand breaks. Without O<sub>2</sub>, the reduction was smaller. On a molar basis, CA was more efficient than MPG, and better protection was obtained with an incubation time of 10 min. However, after correction for the toxic effects of CA, the best protection occurred after 25 min of incubation. Treatment of the cells with 5 μg/ml quinacrine 40 min before radiation in O<sub>2</sub> (39 Gy) or in anoxia (91 Gy) increased the initial yields of breaks in CA-treated and untreated cells by about 1.6 in O<sub>2</sub> and 1.2 without O<sub>2</sub>. The protective effect of CA was decreased only slightly. In experiments to determine the effect of CA on postirradiation repair of radiation-induced breaks, cells were exposed to 39 Gy (with or without O<sub>2</sub>) and then to 5, 20, or 50 mM CA. CA inhibited the rejoining of strands in the presence and absence of O<sub>2</sub>. With a 60-min incubation and at 50 mM, CA not only inhibited rejoining but clearly enhanced break production. (23 refs.)

78-0826 **Some Long-Term Effects of Negative Pions in Mice Exposed to Partial Body Irradiation.** (Eng) Coggle, J. E. (Dept. Radiobiology, Medical Coll. St. Bartholomew's Hosp., Charterhouse Square, London EC1M 6BQ, England). *Br J Radiol* 50(597): 658-662; 1977.

The life-shortening effects of negative pion and <sup>60</sup>Co γ-radiation to the head and upper part of the body of 1-day-old mice were investigated. The mice were exposed to 0, 40 (plateau), 60 (peak), 136 (plateau), or 200 (peak) rads of negative pions or 0, 40, 60, 100, 200, or 300 rads of <sup>60</sup>Co γ rays. The differences between the responses of each sex were negligible. Pions reduced survival approx 6.8% for every 100 rads; the value for β rays was 5.7%/100 rads. Concerning relative biological effectiveness (RBE), pions are about 1.3 times more effective than <sup>60</sup>Co γ rays at reducing the life span of 1-day-old mice by 10 wk; at lower doses, however, the RBE of pions may be higher, reaching a value of 2 for 6 wk of life-shortening. The tumor incidence rate at all ages was greater in mice receiving peak doses of pions and in those given the higher doses of γ rays. (17 refs.)

78-0827 **Mast Cells and Eosinophilic WBC During the Development of Mammary Gland Neoplasms in**



**Female Rats  $\gamma$ -Irradiated at the Age of 4 Wk. (Rus.)** Oshchepkov, A. B. (Moscow, USSR). *Biull Eksp Biol Med* 84(7): 84-86; 1977.

A study was made of the effect of whole-body  $\gamma$ -irradiation (200 rads, dose rate 232 rads/min) of random-bred female rats at the age of 4 wk on the mast cells and eosinophilic WBC of the breast tissue. The first breast neoplasm was discovered 6 mo after irradiation, 2 tumors were found among 6 animals sacrificed after 12 mo, 4 tumors were found among 10 rats sacrificed after 15 mo. The first breast tumor was found in a rat aged 15 mo in the control group. All tumors were benign. Tumor formation was preceded by hyperplasia in the irradiated group, but the control animals developed tumors against a background of hyperplasia or mastopathy. Irradiation caused a considerable increase in the mast cell count in the breast tissue; it peaked on the 14th day, after which it declined gradually to control levels during the third to fourth months. This reduction in the mast cell count coincided with the development of epithelial hyperplasia, and a further reduction was seen after 6 mo, ie at the time of tumor formation. Irradiation caused a significant increase in the eosinophil count of the breast tissue. The findings indicate major roles for disturbances in eosinophil count, which probably indicate the accumulation of estrogens in the mammary tissue, and for changes of mast cell count in the genesis of radiation-induced mammary gland tumors. (10 refs.)

**78-0828 Irradiation-induced Erythroleukemia and Myelogenous Leukemia in the Beagle Dog: Hematology and Ultrastructure.** (Eng) Seed, T. M. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL 60439); Tolle, D. V.; Fritz, T. E.; Devine, R. L.; Poole, C. M.; Norris, W. P. *Blood* 50(6): 1061-1079; 1977.

Continuous whole-body exposure to  $^{60}\text{Co}$ - $\gamma$  irradiation induced a high incidence of leukemia in adult beagle dogs. At 5, 10, and 17 R/day (22-hr exposure), 20/53 animals died from myelogenous leukemia (15) or erythroleukemia (5), the latter deaths occurring only at the lowest dose. Consistent preclinical changes in the peripheral blood included (1) a partial recovery from an initial severe leukopenia, (2) a prolonged accommodation-to-irradiation phase, and (3) marked oscillations in platelet values in the preleukemic period. In the terminal phase, the dogs were severely anemic, thrombocytopenic, and commonly leukopenic. Peripheral blood buffy coat preparations contained circulating blast cells and juvenile forms. The RBC and platelet morphology was consistently abnormal. The bone marrow was altered most severely; other organs showed variable degrees of leukemic infiltration and proliferation and loss of normal tissue architecture. The marrow was hyperplastic, with little or no fat remaining. Differential marrow cell counts showed increased numbers of immature cell forms. Myeloid/erythroid ratios ranged from 2.6:1 to 61.5:1 in the granulocytic leukemias and 0.2:1 to 1:1 in the erythroleukemias. Juvenile leukemic cells (both circulating and tissue

forms) displayed asynchronous patterns of nuclear cytoplasmic maturation, increased incidence of nuclear clefts, coalescence of cytoplasmic granules, and bizarre arrangements of endoplasmic reticulum. These experimentally induced canine leukemias have many hematologic and cytologic features in common with both spontaneous and radiation-induced leukemias of man. Thus, they may provide a useful model for the study of human leukemia. (50 refs.)

**78-0829 Effects of Endocrinologic Conditions Associated with Acute Versus Chronic Lactation on the Incidence of Mammary Carcinomas in Irradiated Rats.** Brief Communication. (Eng) Gould, M. N. (Argonne Natl. Lab., Div. Biological and Medical Res., 970 Cass Ave., Argonne, IL 60439); Clifton, K. H.; Crowley, J. *J Natl Cancer Inst* 60(2): 469-471; 1978.

An experiment was designed to determine the relationship between hormone states that promote or inhibit lactation and the incidence of mammary carcinoma(s) (MC). Five groups of female Fischer rats were subjected to various combinations of the following treatments: (1) adrenalectomy; (2) id inoculation with 0.05 ml of a 50% cell suspension of the mammary tropic pituitary tumor MtTF4, which secretes large amounts of prolactin and lesser amounts of ACTH and growth hormone; (3) cortisol, 3 mg/day, sc; and (4) irradiation with 500 rads of  $^{137}\text{Cs}$   $\gamma$ -rays. Group A rats received 1,2,3,4; Group B, 1,2,4; Group C, 2,4; Group D, 1,2,3; Group E, 1,2,3,4. The chronically lactating rats, Group C and E, did not develop MC. However, rats that did not lactate (Group B) or those that lactate acutely at the time of irradiation (Group A) developed MC, to a similar extent there were 18 MC in 10/14 rats in Group B, 16 MC in 8/16 rats in Group A. Apparently, glucocorticoids do not interfere with the initiating step in mammary carcinogenesis. In Group D, maintenance of chronically high glucocorticoid levels in irradiated rats with high prolactin levels reduced the incidence of MC to 3 in 3/15 rats. (12 refs.)

**78-0830 Investigations on Supercoiled DNA in Various Rat Cells.** (Eng) Egg, D. (Medizinische Universitätsklinik, A-6020 Innsbruck, Austria); Altmann, H.; Günther, R.; Topaloglou, A. *Exp Pathol (Jena)* 14(6): 291-296; 1977.

The effect of radiation-induced single-strand breaks in nuclear DNA and their repair on the sedimentation properties of nucleoids from Sprague-Dawley rat spleen and thymus cells and rat Yoshida tumor cells was investigated. Low-dose  $\gamma$  radiation used to induce the breaks. The sedimentation velocity of nucleoids obtained by lysing cells with nonionic detergents in high salt concentrations was a function of the



ding pattern of the nuclear DNA. Loss of superhelical ns by irradiation decreased the sedimentation coefficient. doses of about 1,000 rads, all supercoils appeared to be t, and higher doses were almost ineffective. Ethidium bro- de intercalation removed negative superhelical turns from e DNA. Further intercalation probably caused a folding of e DNA molecules, as indicated by an increase in the sedi- mentation rate. Irradiation damages were repaired faster in tumor cells than in the spleen and thymus cells. The limination rate of nucleoids from organs of whole-body- radiated rats was comparable to that of in vitro-irradiated cleoids. The repair of radiation-induced single-strand aks in Yoshida cell DNA was delayed in the presence of prostaglandin E<sub>2</sub> (1 µg/ml). These findings indicate that any ibition of DNA repair is connected with an increased risk inducing mutations. (17 refs)

0831 **The Sensitising Effect of a Sunscreening Agent, p-Aminobenzoic Acid, on Near UV Induced Damage in a Repair Deficient Strain of *Escherichia coli*.** (Eng) Hodges, N. D. (Sch. Pharmacy and Pharmacology, Univ. Bath, Bath, Avon, England); Moss, S. H.; Davies, D. *Photochem Photobiol* 26(5): 493-498; 1977.

model bacterial system involving the repair-deficient *Escherichia coli* strain K12 AB2480 *uvr A6, recA13* was used to show that the sunscreening agent p-aminobenzoic acid (PABA) may also sensitize cells to the formation of UV-induced lesions in the DNA, which may be linked to increased skin cancer production. Following exposure of the bacteria to 313-nanometer (nm) UV light, the inactivation instant increased at PABA concentrations ranging from 0 to 0.05%; it then decreased with increasing concentrations up to 0.5%. Thus, PABA can sensitize or protect cells against 313 nm radiation depending on concentration. Control experiments demonstrated that this sensitization was photochemical in nature. Therefore, at concentrations up to approx 0.05%, PABA increased the sensitivity of this *E. coli* strain to inactivation by 313 nm radiation; only at concentrations > 0.35% did the compound exert a sufficient light-protecting effect to counteract the sensitizing effect and produce an overall protective effect against DNA damage. In preliminary experiments using the selective action of photoenzymatic repair, the sensitization to near UV radiation was found to be partially due to an increased formation of pyrimidine dimers. It is suggested that other topically applied chemicals, especially sunscreening agents, be studied for sensitizing effects on the induction of DNA damage by light. (17 refs.)

0832 **Typical Xeroderma Pigmentosum Complementation Group A Fibroblasts Have Detectable Ultraviolet Light-induced Unscheduled DNA Synthesis.** (Eng) Ling, R. A. (Dermatology Branch, NCI, NIH, Bethesda, MD 20014); Andrews, A. D.; Tarone, R. E.; Robbins, J. H.

*Biochim Biophys Acta* 479(4): 400-410; 1977.

The presence of UV-induced unscheduled DNA synthesis in four xeroderma pigmentosum complementation group A fibroblast cell line [XP12BE (CRL 1223), XP1LO (CRL 1201), XPKFSF (CRL 1206), and XP25RO (CRL 1261)] was investigated. The cells were irradiated with 25 joules (J)/m<sup>2</sup> of 254-nanometer UV light at an incident flux of 0.17 J/m<sup>2</sup>/sec. <sup>3</sup>H-thymidine incorporation following irradiation indicated that the cells have unscheduled DNA synthesis at 0.4% to 1.3% of the normal rate; this probably reflects repair replication of DNA excision repair. Addition of 10<sup>-2</sup> M hydroxyurea did not abolish the UV-induced DNA synthesis. Planimetric studies showed the nuclear area was not increased in any of the irradiated cell lines. It is not known if this induced synthesis in any of the strains is a normal excision process, the result of the function of a decreased effective amount of a normal gene product, or the result of an abnormal gene product. (26 refs.)

78-0833 **Molecular Mechanisms of Induced Mutagenesis. Replication In Vivo of Bacteriophage  $\phi$  X174 Single-stranded, Ultraviolet Light-irradiated DNA in Intact and Irradiated Host Cells.** (Eng) Caillet-Fauquet, P. (Departement de Biologie Molculaire, Universite Libre de Bruxelles, Rue des Chevaux 67, B 1640 Rhode St Genese, Belgium); Defais, M.; Radman, M. *J Mol Biol* 117(1): 95-112; 1977.

The extent of DNA synthesis on  $\phi$ X174 Aam18 templates containing UV-induced photolesions was studied in both intact and irradiated (HF4733 and HF4704) *Escherichia coli* cells. The photolesions were induced by irradiation (0.2 Jm<sup>-2</sup>sec<sup>-1</sup>) of phage suspensions. UV-induced lesions in the viral DNA caused a permanent blockage of DNA synthesis in intact cells. However, when the host cells were irradiated and incubated to fully induce the error-prone repair system, a significant fraction of irradiated  $\phi$ X174 DNA molecules could be fully replicated. Thus, inducible error-prone repair in *E. coli* is manifested by an increased capacity for DNA synthesis on damaged viral DNA. Addition of 100 µg chloramphenicol inhibited this inducible DNA synthesis. It is suggested that UV-induced mutagenic repair of single-stranded  $\phi$ X174 DNA might be the result of an erroneous DNA synthesis. The process could involve either an unknown inducible DNA polymerase and/or result from a modification of the normal DNA replication machinery. (45 refs.)

78-0834 **UV-induced Unscheduled DNA Synthesis in Guinea Pig Skin Melanocytes Isolated in Cul-**



ture. (Eng) Moreno, G. (Institut de Pathologie Cellulaire, Unite 48 INSERM, Hopital de Bicetre, Paris, France); Vinzens, F.; Prunieras, M. *J Invest Dermatol* 70(1): 21-24; 1978.

UV light-induced unscheduled DNA synthesis (UDS) was examined in melanocytes isolated from the epidermis of guinea pig ears. UDS occurred in virtually all melanocytes following irradiation of the cells with 5, 10, or 50 joules/m<sup>2</sup>. However, UDS was lower in the melanocytes than in guinea pig fibroblasts and keratinocytes. (32 refs.)

**78-0835 Changes Induced by Ultraviolet Light in the Superhelical DNA of Lymphocytes from Subjects with Xeroderma Pigmentosum and Normal Controls.** (Eng) Cook, P. R. (Sir William Dunn Sch. Pathology, Univ. Oxford, South Parks Road, Oxford OXI 3RE, England); Brazzell, I. A.; Pawsey, S. A.; Giannelli, F. *J Cell Sci* 29: 117-127; 1978.

Repair of UV-damaged DNA was investigated in lymphocytes from four xeroderma pigmentosum (XP) patients (groups A, C, D, and an XP variant), and the findings were compared with those of normal controls. In preliminary experiments, the nucleoids from untreated XP patients and normal controls behaved identically on sucrose gradient centrifugation, indicating that the integrity and degree of supercoiling of their DNA were similar. Lymphocytes were then irradiated with 9.6 joules/kg  $\gamma$  radiation and incubated for various periods. The irradiated nucleoids sedimented at about one-third the rate of their unirradiated counterparts. Incubating irradiated cells at 37 C increased their sedimentation rate as the DNA was repaired, so that at 5 hr, the rate was almost that of unirradiated controls. In another experiment, cells from XP patients were irradiated with 2.5 joules/m<sup>2</sup> UV radiation and incubated for various periods of time, and the DNA sedimentation rates were examined. Following irradiation, the nucleoids sedimented rapidly, indicating that the cells were unable to incise normally, so that the nucleoids retained their supercoiling. However, cells from the XP variant and an XP heterozygote had sedimentation rates similar to those of controls. They were thus capable of normal levels of incision with consequent release of supercoiling. (30 refs.)

**78-0836 Effect of Pre-treatment with 5-Bromouracil in an Ultraviolet Sensitive Strain of *Neurospora crassa*.** (Eng) Nemerofsky, A. (Dept. Biology, State Univ. New York, New Paltz, NY, 12561). *Genet Res* 30(3): 265-271; 1977.

The effect of pretreatment with 0.41 mg 5-bromouracil (5-BU) on the mutation frequency in a UV-sensitive strain of *Neurospora crassa* (*uvr-2*) was determined. The conidia were irradiated with a UV source at a rate of 0.8 joule/m<sup>2</sup> to a total dose of up to 86.4 joules/m<sup>2</sup>. 5-BU enhanced the mutation frequency in these conidia. Since a similar effect was noted at the *rib-1* locus, which is not UV-sensitive, the error-prone repair mechanism may be related to postreplication repair. The enhancement may be due to the interference of 5-BU with this repair. The max increase in mutation frequency probably occurs when the greatest number of unrepaired premutational UV lesions are repaired in the presence of 5-BU. (18 refs)

**78-0837 Penetration of the Small Intestinal Mucosa by Asbestos Fibers.** (Eng) Storeygard, A. R. (Duke Univ. Medical Center, Durham, NC); Brown, A. L. *Mayo Clin Proc* 52(12): 809-812; 1977.

Four to 5 ml of an amosite asbestos solution containing  $9 \times 10^9$  fibers/ml was injected into an isolated section of Sprague-Dawley rat jejunum in vivo. After 1 hr, fibers (all > 5  $\mu$ m long) had penetrated the epithelial cells in 3 of 5 exposed rats. They were also present in the lamina propria. There was no predilection for a particular cell type, and all fibers entered at the luminal surface. (10 refs.)

See also:

\*(Rev.): 78-0635, 78-0638, 78-0639, 78-0640, 78-0666

\*(Chem.): 78-0769, 78-0804, 78-0806, 78-0807.

\*(Viral): 78-0854, 78-0855.

\*(Path.): 78-0998.

\*(Epid-Biom.): 78-1083, 78-1087, 78-1096, 78-1099, 78-1108, 78-1121, 78-1125, 78-1127



## VIRAL CARCINOGENESIS

**0838 In Vitro Synthesis and Characterisation of Full- and Half-Genome Length Complementary DNA in Avian Oncoviruses.** (Eng) Lai, M. M. (Dept. Microbiology, Univ. Southern California, Sch. Medicine, Los Angeles, CA, 90033); Hu, S. S. *Nature* 271(5644): 481-483; 1978.

Full- and half-genome-length complementary DNA (cDNA) was synthesized in vitro from the Schmidt-Ruppin strain of Rous sarcoma virus (RSV), subgroup D. The optimum concentration of Triton X-100 was determined individually for each virus preparation. The minimum concentration of viral proteins for efficient synthesis of large cDNA was 1 mg/ml. A sucrose gradient analysis of the synthesized product revealed that 10%-20% of the DNA synthesized had a sedimentation velocity greater than or equal to that of a simian virus 40 (SV40) DNA marker (mol wt  $1.65 \times 10^6$ ). This DNA represented almost full-genome-length cDNA molecules. At least 1  $\mu$ g cDNA could be synthesized from 5 mg of purified virus. Another peak had a sedimentation coefficient roughly equivalent to that of denatured SV40 DNA, and it represented half-genome-length molecules. Some of the molecules formed single-stranded circular molecules with a distinct secondary structure. DNA molecules of mol wt  $1.5 \times 10^6$  contained only complementary sequences, but shorter DNA fragments contained both (+) and (-) strands. The full-length cDNA probably resulted from initiation at the 5' site, a jump to 3', and 3'-5' synthesis; the shorter fragments probably resulted from early termination of this synthesis. (20 refs)

**0839 Occurrence of Partial Deletion and Substitution of the *src* Gene in the RNA Genome of Avian Sarcoma Virus.** (Eng) Lai, M. M. (Dept. Microbiology, Univ. Southern California, Sch. Medicine, Los Angeles, CA 90033); Hu, S. S.; Vogt, P. K. *Proc Natl Acad Sci USA* 74(11): 4781-5; 1977.

Acrylamide gel electrophoresis was used to examine the genome size of 20 transformation-defective (*td*) viruses from different strains of Rous sarcoma virus (RSV), including Prague-subgroups A and C, Carrer subgroup D, Schmidt-Ruppin subgroups A and SR-A, D), and Bratislava 77, to see if they all have the same size *src* deletion and a uniform structure. Isolates except those from SR-D had class B RNA (35S). The *td*SR-D viruses could be classified into two groups: one with an extensive deletion of the *src* gene and one with a smaller deletion, retaining about 25% of the gene. However, the RNase T<sub>1</sub>-oligonucleotide fingerprints of all *td*

SR-D viruses were identical, lacking two sarcoma-specific oligonucleotides. A minor nucleotide was also noted at low concentrations in all SR-D viruses. It was not possible to determine whether the *src* gene was deleted to a smaller extent in some of the *td*SR-D isolates or whether the deletion was identical with other sequences being acquired. Heteroduplex studies, however, suggested that the 35S RNA of all deletion mutants of SR-D were of full genome length. Deletion loops of 2.0 and 1.5 kilobases, respectively, were noted for wild-type SR-D and 35S RNA of *td*SR-D viruses. Furthermore, some heteroduplexes with a substitution loop of 0.6 to 0.7 kilobase at the same site as the deletion loop were observed in all five *td*SR-D viruses. It is concluded that some of the *td*SR-D viruses have a partially deleted *src* gene and that all of the *td*SR-D viruses have incorporated heterologous sequences of distinct length in some RNA molecules at the position of the *src* gene. Various mechanisms for the acquisition of the heterologous sequences are discussed. (23 refs.)

**78-0840 Immunologic Identification of Fetal Calf Serum-derived Proteins on the Surfaces of Cultured Transformed and Untransformed Rat Cells.** (Eng) Phillips, E. R. (Lady Davis Inst. Med. Res., Jewish General Hosp., 3755 Cote St. Catherine Road, Montreal, Quebec H3T 1E2, Canada); Perdue, J. F. *Int J Cancer* 20(5): 798-804; 1977.

The antigens of W/Fu rat embryo fibroblasts and rat Rous sarcoma cells were studied by nonionic detergent solubilization of radiolabeled cells. Solubilized antigens were complexed with rat immune IgG and the complexes were precipitated with rabbit anti-rat IgG. The precipitated radiolabeled antigens were then dissolved in sodium dodecyl sulfate and separated by polyacrylamide gel electrophoresis. The investigation revealed the existence of cell-surface antigenic proteins that were derived from the fetal calf serum (FCS) used in the culture medium. These FCS-dependent antigens included at least three molecular species with approx mol wts of 95,000, 80,000, and 68,000 daltons. One of these proteins (95,000 daltons) adhered to the cell surface so tenaciously that a trace amount remained even after subculture in the absence of FCS. The highly transformed Rous sarcomas bound little or none of this protein to their surfaces, but untransformed rat embryo fibroblasts bound large quantities. A rat Rous sarcoma line intermediate in morphological transformation bound an intermediate amount of this antigen. These findings suggest that the interaction of certain serum components with



the cell surface may be related to plasma membrane properties that distinguish untransformed and transformed cells. (18 refs.)

**78-0841 Determinants of Glycolytic Rate in Normal and Transformed Chick Embryo Fibroblasts.** (Eng)

Fagan, J. B. (Lab. Molecular Biology, NCI, Bethesda, MD, 20014); Racker, E. *Cancer Res* 38(3): 749-758; 1978.

The increased glycolysis rate in C/O chick embryo fibroblasts transformed by Rous sarcoma virus, subgroup A, was investigated. In both normal and transformed cells, the regeneration of ADP and orthophosphate (Pi) was the rate-limiting factor for glycolysis. The plasma membrane Na-K-ATPase was a major contributor to the ADP and Pi regeneration in the fibroblasts, but its contribution was not changed by viral transformation. Neither protein nor nucleic acid synthesis nor microtubular function contributed significantly to the ADP and Pi pools required for glycolysis before or after transformation. Neither oxidative phosphorylation nor ATPase activity of isolated mitochondria could account for the increased rate of glycolysis following transformation. Culturing fibroblasts in the presence of ATPase activators mimicked some of the characteristic changes induced by viral transformation: the apparent  $K_m$  of glycolysis was decreased by a factor of 10, and the apparent  $V_{max}$  of hexose transport was increased by a factor of 4. However, ATPase activators did not change the apparent  $V_{max}$  of glycolysis or the apparent level of hexokinase, and the morphological and growth characteristics of transformed cells were not mimicked. (31 refs)

**78-0842 Rous Sarcoma Virus p19 Binds to Specific Double-stranded Regions of Viral RNA: Effect of p19 on Cleavage of Viral RNA by RNase III.** (Eng) Leis, J. P. (Dept. Surgery, Duke Univ Medical Center, Durham, NC, 27710); McGinnis, J.; Green, R. W. *Virology* 84(1): 87-98; 1978.

The binding of two group-specific antigens, p19 and p12, of Rous sarcoma virus (RSV, Prague-C) to various RNA's was measured by a sensitive nitrocellulose filter binding assay capable of detecting binding reactions with association constants as low as  $3 \times 10^6$  liters/mole. RSV p19 bound preferentially to specific double-stranded RNA regions, since (1) the association constant for Neurospora nuclease-digested 34S RNA was the same as that for untreated RNA; (2) the association constant for 34S RNA partially digested with *Escherichia coli* RNase III (which is specific for double-stranded RNA regions) was thirtyfold lower than that for untreated RNA; (3) p19 prevented cleavage of 34S RSV-RNA by *E. coli* RNase III; and (4) p19 bound cell precursor RNA's containing RNase III-sensitive sites, but not mature RNA's lacking these sites. In contrast, purified RSV p12

bound all RNA's tested with association constants roughly proportional to their mol wt. The possible role of p19 in regulating messenger RNA concentrations and viral RNA translation is discussed. (31 refs.)

**78-0843 Nucleotide Sequence of Rous Sarcoma Virus RNA at the Initiation Site of DNA Synthesis**

**The 102nd Nucleotide is U (Letter to Editor).** (Eng) Coffin J. M. (Dept. Molecular Biology and Microbiology, Tufts Univ. Sch. Medicine, Boston, MA, 02111); Haseltine, W. A. *J Mol Biol* 117(3): 805-814; 1977.

The nucleotide sequence of Rous sarcoma virus RNA that spans the primer binding site and the point of initiation of DNA synthesis was investigated. The sequence of (C<sub>2</sub>U<sub>2</sub>) A U-U-U-G found corresponds to the d(A-A-T-G-A-A-G) sequence at the 5' end of the transfer RNA-Trp primer. Therefore, the nucleotide opposite the terminal A of the primer is the complementary U. No internal repetition of > 30 nucleotides of the 5' end could be detected. Thus the 3'-terminal A-OH residue of the transfer RNA-Trp primer can be base paired with the template RNA molecule. (21 refs)

**78-0844 The B Locus (MHC) in the Chicken: Association with the Fate of RSV-induced Tumors**

(Eng) Collins, W. M. (Dept. Animal Sciences, Univ. New Hampshire, Durham, NH 03824); Briles, W. B.; Zsigray, R. M.; Dunlop, W. R.; Corbett, A. C.; Clark, K. K.; Marks, J. L.; McGrail, T. P. *Immunogenetics* 5(4): 333-343; 1977.

The fate of tumors induced by Rous sarcoma virus (RSV) was determined in an F<sub>2</sub> population segregating at three alloantigen loci. The F<sub>1</sub> generation resulted from crossing tumor resistant RPRL Single Comb White Leghorn line 6 ( $B^2B^2/D^3D^3/I^2I^2$ ) with tumor-susceptible RPRL Single Comb White Leghorn line 15<sub>1</sub> ( $B^5B^5/D^4D^4/I^6I^6$ ). Of 697 chickens inoculated with RSV (0.5 ml of a 10<sup>7.5</sup> dilution), 692 developed a tumor. Among the F<sub>2</sub> segregants  $B^2B^2$ ,  $B^2B^5$ , and  $B^5B^5$ , the percentage of chickens dying of terminal tumors by 70 days after inoculation was 5%, 26% and 93%, respectively. Neither *D* or *I* genotypes nor sex significantly affected tumor growth. The incidence of metastatic tumors in chickens that died with tumors was also significantly associated with the *B* genotypes. It is concluded that the *B* locus, the avian counterpart to the major histocompatibility locus in other species, plays a major role in determining the outcome of RSV-induced tumors in chickens. (61 refs.)

**78-0845 Effect of Tunicamycin on the Morphogenesis of Semliki Forest Virus and Rous Sarcoma Virus**



**Report.** (Eng) Ogura, H. (Dept. Biochemistry, Cancer Okayama Univ., Medical Sch., Okayama 700, Japan); Idt, M. F.; Schwarz, R. T. *Arch Virol* 55(1/2): 155-159;

iki Forest virus (SFV)-infected chick embryo cells) incubated in the presence of tunicamycin, a drug that specifically inhibits glycosylation, were studied electron microscopically. No extracellular virions were produced, but cellular viral nucleocapsids in paracrystalline form were detected. Under these conditions, types 1 and 2 cytopathic effects, as well as membranous spherules at the plasma membrane, could still be observed. When incubated for 24 hr in the presence of tunicamycin (1 µg/ml), CEC produced by SFV-infected and transformed by Rous sarcoma virus still showed budding and extracellular particles. Intracellular nucleocapsid structures could not be detected. (16 refs.)

**846 In Vitro Transcription of the Avian Oncornavirus Genome by the RNA-directed DNA Polymerase: Analysis of DNA Transcripts Synthesized in Reconstructed Enzymatic Reactions.** (Eng) Collett, M. S. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Faras, A. J. *J Virol* 22(1): 86-96; 1977.

RNA products synthesized in vitro in reconstructed reactions containing purified avian myeloblastosis virus genome and RNA-directed DNA polymerase. The results indicate that (1) the initial DNA product synthesized on either RNA or reconstituted 35S RNA tryptophan transfer RNA (tRNA-trp) template-primer complexes in the presence of low concentrations of deoxynucleoside triphosphates consisted of several discrete size classes, none of which exceeds 100 nucleotides in length; (2) large DNA transcripts (about 1000 nucleotides) can be synthesized on both 70S RNA and 35S RNA tRNA-trp complex by increasing the deoxynucleoside triphosphate concentration; and (3) DNA synthesized by detergent-disrupted virus is considerably longer than DNA synthesized in reconstructed reactions. (35 refs.)

**847 Establishment of Marek's Disease Lymphoblastoid Cell Lines from Transplantable Versus Primary Lymphoma.** (Eng) Calnek, W. (Dept. Avian and Domestic Animal Medicine, New York State Coll. Veterinary Medicine, Ithaca, NY 14853); Murthy, K. K.; Schat, K. A. *J Cancer* 21(1): 100-107; 1978.

Establishment of six new Marek's disease lymphoblastoid cell lines in medium containing 2-mercaptoethanol is reported. Four types of materials were used to seed the primary cultures: six spleen cell suspensions from Marek's disease virus (MDV)-infected chickens; buffy coat cells from leukemic chickens; 28 primary tumor suspensions from 3 naturally infected and 25 experimentally infected chickens; and 4 MD

tumor transplants. Only 1/28 lymphomas produced a cell line. Two of seven low-passage and 2/2 established MD transplantable lymphomas grew readily in vitro. The sixth line was obtained using buffy coat cells from a leukemic chicken. Comparative features of the new and previously described cell lines are listed. (38 refs.)

**78-0848 Ultrastructural Studies of Cell-Virus Interaction in Reptilian Cell Lines. IV. Effects of Chloramphenicol and Ethidium Bromide on VSW Cell Mitochondria and Associated Virions.** (Eng) Lunger, P. D. (110 Wolf Hall, Newark, DE 19711); Klettmann, W.; Clark, H. F. *Acta Virol (Praha)* 21(5): 375-382; 1977.

The structural effects of chloramphenicol (CAP) and ethidium bromide (EB) on VSW cell (derived from the spleen of a tumor-bearing viper) mitochondria and intramitochondrial virions (IMV) were studied by thin-section electron microscopy. CAP-treated cells showed a wide variety of mitochondrial alterations, notably, swelling of the organelles and loss of cristae orientation. In general, the IMV were severely disrupted, particularly in the peripheral regions. Strandlike material radiated from the shell zone to the adjacent cristae-matrix area. EB-treated cells also displayed considerable mitochondrial distortion, evidenced primarily by the formation of small, localized, multimembranous regions. However, IMV exposed to EB showed less structural damage than CAP-treated ones. The relative incidence of IMV production was approx fourfold higher in EB-treated cells than in CAP-treated cells, suggesting that virion synthesis may be under nuclear, rather than mitochondrial, control. (35 refs.)

**78-0849 Macromolecular Synthesis in Cells Infected by Frog Virus 3. VIII. The Nucleus Is a Site of Frog Virus 3 DNA and RNA Synthesis.** (Eng) Goorha, R. (Div. Virology, St. Jude Children's Res. Hosp., P.O. Box 318, Memphis, TN, 38101); Murti, G.; Granoff, A.; Tirey, R. *Virology* 84(1): 32-50; 1978.

To elucidate the role of the nucleus in frog virus 3 (FV 3) replication, viral DNA and RNA synthesis in infected cells was studied by electron microscopic autoradiography and biochemical techniques. Approx 30% of the viral DNA and RNA was synthesized in the nucleus and then transported into the cytoplasm. Both nuclear and cytoplasmic DNA appeared within 1-2 hr of infection. The mol wt of the newly synthesized viral DNA did not exceed  $8 \times 10^6$ , as measured by sedimentation in alkaline sucrose gradients. In contrast, the cytoplasmic DNA sedimented at a rate expected for a single strand of the viral genome ( $50 \times 10^6$  daltons). Pulse-chase experiments indicated a precursor-product relationship between the nuclear and cytoplasmic DNA: about 35% of the nuclear DNA was chased into the cytoplasm and was



genome size at the end of a 4-hr chase. Nuclear viral DNA synthesis was more sensitive to cycloheximide than cytoplasmic viral DNA synthesis. Thus, initiation of viral DNA replication apparently takes place in the nucleus, with elongation, ligation, and/or maturation occurring in the cytoplasm. (27 refs.)

- 78-0850 Cellular RNA Synthesis in Normal and Mengovirus-infected L-929 Cells.** (Eng) Apriletti, J. W. (Dept. Biochemistry, Univ. California, Berkeley, Berkeley, CA, 94720); Penhoet, E. E. *J Biol Chem* 253(2): 603-611; 1978.

Cellular RNA synthesis was studied in uninfected and mengovirus-infected mouse L-929 cells. RNA polymerases I, II, and III were partially purified, and their chromatographic properties were analyzed by diethylaminoethyl-Sephadex A-25 chromatography. The subunit structure of the RNA polymerase II from normal and virus-infected L-929 cells was compared with that of mouse liver RNA polymerase II. Mengovirus infection did not affect the levels of host RNA polymerase activities, nor did it alter the subunit composition of RNA II polymerase. Further experiments revealed that mengovirus inhibited the endogenous RNA polymerase activity in the chromatin of infected cells; however, the residual activity responded normally to stimulation by ammonium sulfate, heparin, and Sarkosyl. The template capacity of the chromatins was then compared with added RNA polymerase II and by a rifampicin challenge assay using *Escherichia coli*. Identical results were obtained in each case. Analysis of RNA chain-elongation rates and the number of growing chains in the nuclei and chromatin showed that mengovirus decreased the number of RNA polymerase II molecules synthesizing RNA without altering the chain-elongation rates of the remaining, active molecules. (46 refs)

- 78-0851 Cyclic AMP Regulation of Mammary Tumor Virus Production.** (Eng) Yang, J. (Cancer Res. Lab., Univ. California, Berkeley CA 94720); Nandi, S. *J Virol* 21(2): 815-819; 1977.

In short-term primary cultures of BALB/cfC3H mouse mammary tumors, glucocorticoid-stimulated production of murine mammary tumor virus (MTV) was enhanced two- to threefold by the addition of dibutyryl cyclic AMP (cAMP) and agents (isoproterenol and epinephrine) that stimulate adenylate cyclase activities. The cAMP potentiation seemed to depend on the level of MTV stimulation elicited by the glucocorticoids (hydrocortisone and dexamethasone) alone. Although the glucocorticoids increased MTV production five- to tenfold over basal levels, their effects varied according to cell density. When glucocorticoid-stimulated virus production was suboptimal, cAMP restored the max stimulatory effect of the glucocorticoids. (30 refs.)

- 78-0852 Synthesis and Processing of Precursor Polypeptides to Murine Mammary Tumor Virus Structural Proteins.** (Eng) Racevskis, J. (Memorial Sloan Kettering Cancer Center, New York, NY 10021); Sarkar, H. *J Virol* 25(1): 374-383; 1978.

The intracellular synthesis of murine mammary tumor virus (MuMTV) proteins was studied, and the precursor polypeptides of the MuMTV structural proteins gp47 and p27 were identified by the MuMTV-producing epithelial cell line MuMT-73. These studies were performed with immunoprecipitation techniques using monospecific antisera to gp47 and p27 and high-resolution polyacrylamide gel electrophoresis. In pulse-labeling experiments using <sup>35</sup>S-methionine monospecific antisera to p27 precipitated a 75,000 mol wt protein as the major intracellular component. Analysis of the same cellular extracts with monospecific antisera to gp47 revealed a 70,000-dalton precursor. After chase periods, there was a loss of label from the precursors and a concomitant increase of labeled extracellular mature viral proteins. The glycoprotein precursor incorporated labeled glucosamine and was processed twice as fast as the p27 precursor. The results indicate that gp47 and p27 are initially synthesized as products of two separate high-mol-wt precursor polypeptides. The findings, together with previous findings with MuMTV and C-type RNA tumor viruses, suggest that noncoordinate synthesis of viral structural proteins, via independently synthesized high-mol-wt precursors, might be a general characteristic of all RNA tumor viruses. (30 refs.)

- 78-0853 RNase H and RNA-directed DNA Polymerase Associated Enzymatic Activities of Murine Mammary Tumor Virus.** (Eng) Dion, A. S. (Inst. Medical Res., Camden, NJ 08103); Williams, C. J.; Moore, D. H. *J Virol* 22(1): 187-193; 1977.

The RNA-directed DNA polymerase (RDDP) of murine mammary tumor virus, a B-type RNA tumor virus, was purified sequentially through diethylaminoethyl-cellulose phosphocellulose (step gradient), and phosphocellulose (linear salt gradient) chromatography followed by glycerol sedimentation centrifugation. During all stages of purification, coincident peaks of RDDP activity, templated by polyribocytidylate-oligodeoxyguanylate, and RNase H digestion of <sup>32</sup>P-polyriboadenylate-polydeoxythymidylate were observed. Both enzymatic activities displayed a cation preference for magnesium. Under conditions that removed adventitious associated nucleases, RNase H activity was found to copurify with polymerase. Substrate-specificity assays indicated that the polymerase-associated RNase H activity was directed only against the RNA strand of an RNA-DNA hybrid. It is highly probable that B-type RNase H and RDDP of the viruses are associated enzymatic activities analogous to those observed for avian and mammalian C-type RNA tumor viruses. (19 refs.)



854 **Increased Synthesis and Expression of H-2 Antigens on Thymocytes as a Result of Radiation-Induced Leukemia Virus Infection: A Possible Mechanism for H-2-Dependent Control of Virus-Induced Neoplasia.** (Eng) Meruelo, D. (Irvington House Inst., New York Univ. Sch. Medicine, 1171 First Ave., New York, NY, 10016); Nimelstein, S. H.; Lieberman, M. P.; Lieberman, M.; McDevitt, H. O. *J Exp Med* 247(2): 470-487; 1978.

The mechanism by which genes linked to the D end of the major histocompatibility complex, H-2, confer resistance to radiation leukemia virus (RadLV)-induced thymoma was investigated. H-2 haplotypes did not influence initial virus replication, but they did alter virus proliferation and survival in the thymocytes. This effect was evident 5 wk after RadLV injection. Furthermore, the cell-surface expression of H-2 antigens increased immediately after injection. Expression of H-2K molecules increased significantly in cells of susceptible and resistant mice. However, significant increases in H-2D antigen expression occurred only on thymocytes of resistant animals. The increased expression of H-2K and H-2D molecules was the result of increased H-2 glycoprotein synthesis, and not the result of 'buried' determinants normally present on the membranes of uninfected thymocytes. The mechanisms in which changes in H-2 antigen expression might influence immune responses to virus infection are discussed. (34 refs.)

855 **Type-C RNA Virus and Leukemogenesis: Lack of Correlation Between Expression of Endogenous, Ecotropic Murine Leukemia Virus and Radiation-Induced Leukemogenesis in Mice.** (Eng) Nagao, K. (Dept. Pathology, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan). *Hiroshima J Med Sci* 26(2/3): 177-188; 1977.

The expression of murine leukemia virus (MuLV) was examined by XC plaque assay in three groups of female ICR/JCL mice (whole-body-irradiated, partial-body-irradiated, or thymectomized and irradiated) exposed to four doses of 170 R x-radiation at 5-day intervals to determine whether the infectivity of C-type RNA viruses is correlated with x-ray-induced leukemia. Thymic lymphomas developed in 20/23 whole-body-irradiated mice. There was particular expression of infectious MuLV in the thymus during leukemogenesis; infectivity patterns and titers in other tissues were also inconsistent with the leukemogenic process. Very high virus titers were detected in the uterus during the entire observation period. Leukemia occurred in 5/34 partial-body-irradiated mice; these cases were thymic, 1 nonthymic. The MuLV infectivity patterns were similar to those of whole-body-irradiated mice, although the five leukemic cases had an ample quantity of infectious MuLV in every tissue; the highest titers occurred in the uterus, thymus, and spleen. Seven of 18 thymectomized, whole-body-irradiated mice developed nonthymic leukemia. MuLV infectivity patterns in the various tissues were

comparable to those in the other two groups, regardless of the efficiency of leukemia induction. It is concluded that there is no apparent etiologic correlation between MuLV expression and radiation-induced leukemogenesis. (33 refs.)

78-0856 **Type-C RNA Virus and Leukemogenesis: Effect of Thymectomy on Leukemogenesis in Rat Adapted Gross Virus (RAGV) Infected Rats.** (Eng) Nagao, K. (Dept. Pathology, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan). *Hiroshima J Med Sci* 26(2/3): 189-194; 1977.

The effect of thymectomy on the development of leukemia and on the murine leukemia virus (MuLV) infectivity pattern was examined in rats inoculated at birth with rat-adapted Gross virus (RAGV). Wistar/Furth rats were given 0.2 ml RAGV sc within 48 hr of birth and thymectomized 3 wk later. The expression of MuLV in various tissues before and after the thymectomy was tested by the XC plaque assay. The incidence of leukemia was not affected by thymectomy, and every rat developed nonthymic lymphatic leukemia. However, during the preleukemic stage, no infectious ecotropic MuLV could be detected in any tissues, including the most likely alternative targets (spleen, bone marrow, and serum). In the leukemic stage, high MuLV titers suddenly appeared in the spleen, bone marrow, and serum. The virus titer remained negative in other tissues throughout the leukemic stage. In some specimens of bone marrow (2/8), mesenteric lymph node (2/2), and liver (2/3) of leukemic rats, MuLV infectivity could not be detected in spite of the histological demonstration of leukemic cell infiltration. These findings suggest that RAGV consists of both ecotropic and xenotropic MuLV and that the latter plays a role in the induction of leukemia in RAGV-infected, thymectomized rats. (25 refs.)

78-0857 **Genetic Analysis of In Vitro Leukemogenesis Induced by Thymus Epithelial Reticulum Cells Transmitting Murine Leukemia Viruses.** (Eng) Haas, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel). *Int J Cancer* 21(1): 115-120; 1978.

In vitro leukemogenesis induced by thymus epithelial reticulum cells transmitting murine leukemia viruses were studied in C57BL/6 (B6), B6-Ly-1.1, and B6-Ly-2.1 mice. When inoculated ip into B6 recipients (one million cells) following their cultivation on leukemic thymus epithelial reticulum monolayers, thymocytes of B6-Ly-1.1 or B6-Ly-2.1 females resulted in tumors in 80% of the mice within 5-6 wk. Most tumors were lymphosarcomas. Immunofluorescence allowed the determination of Ly-1.1, Ly-2.1, and Ly-2.2 antigens. Studies on the origin of the in vitro-induced thymomas indicated that 80% of the tumors were lymphosarcomas carrying the



marker of the cultivated thymocytes. Five of 29 mice inoculated with thymocytes cultivated on leukemic thymus epithelial reticulum monolayers developed tumors thought to be derived from concurrent inoculation of epithelial reticulum cells. Inoculation of 22 mice with monolayer cells resulted in disseminated lymphosarcoma in only 2 mice; the remainder of the tumors were equally divided between reticulum cell neoplasms (type A) and myeloid leukemias. Thus, leukemic thymus epithelial reticulum monolayer cells may themselves be capable of inducing reticulum cell neoplasms and myeloid tumors. (14 refs.)

- 78-0858 Suppression of Murine Leukaemia Virus Production by Ouabain and Interferon in Mouse Cells.** (Eng) Tomita, Y. (Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan); Kuwata, T. *J Gen Virol* 38(2): 223-230; 1978.

The effects of ouabain on the production of murine leukemia virus (MuLV) by K3b and JLS-V9 cells were determined. Addition of 0.1 mM ouabain reduced virus yield from both K3b and JLS-V9 cells by > 50% and 0.5 mM ouabain reduced it by 93% and 89%, respectively, as determined by particle-associated reverse transcriptase activity. However, intracellular reverse transcriptase activity was not altered. Ouabain also reduced the growth rate of these cells up to 81% at a concentration of 0.4 mM. Experiments with 0.5 mM ouabain indicated that MuLV production decreased more rapidly than protein synthesis. K3b cells were also treated with 100 units/ml interferon and 0.5 mM ouabain to determine whether the antiviral action of the former is blocked by the latter. Mouse interferon blocked MuLV production and was not affected by simultaneous ouabain treatment. (23 refs.)

- 78-0859 Nuclear Protein Synthesis and Phosphorylation in Friend Erythroleukemia Cells Stimulated with DMSO.** (Eng) Neumann, J. R. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Housman, D.; Ingram, V. M. *Exp Cell Res* 111(2): 277-284; 1978.

Patterns of nuclear protein synthesis and phosphorylation were investigated in Friend erythroleukemia cells. The rate of incorporation of <sup>3</sup>H-leucine and <sup>32</sup>P-phosphate remained relatively constant during the first 48 hr of dimethyl sulfoxide (DMSO) stimulation, when > 90% of the cells commit to erythroid differentiation, but fell to 20% by 120 hr. Histone H2A phosphorylation was greatly increased during DMSO treatment, but no significant changes were found in the non-histone phosphoprotein patterns, as determined by gel electrophoresis. There was also a small change in the relative amounts of the two subfractions of histone H2A. The most striking change was the overall decrease in protein synthesis and phosphorylation after 50 hr of DMSO treatment. Prior

to this overall decline, there were relative increases in amount and rate of synthesis of the 46,000- and 280,000 dalton proteins. One protein, at 65,000 daltons, appeared to be new and was seen only in autoradiograms, indicating high specific activity of synthesis. The functional significance of these changes, which occur during the commitment time, is not known. (35 refs.)

- 78-0860 Synthesis and Glycosylation of Polypeptide Precursors to the Internal Core Proteins of Friend Murine Leukemia Virus.** (Eng) Evans, L. H. (Dept. Biochemistry, Sch. Medicine, Univ. Oregon Health Sciences Center, Portland, OR 97201); Dresler, S.; Kabat, D. *J Biol Chem* 253(3): 865-874; 1977.

Synthesis of murine leukemia virus (MuLV) protein was studied in STU mouse cells (Eveline cells), which produce large amounts of Friend lymphatic leukemia virus (MuLV). Within 1 min of labeling with L-<sup>35</sup>S-methionine, several different virus-specific proteins antigenically related to the virion core (gag) proteins p12 and p30, which exhibited labeling characteristics of primary translation products, were detected. The most abundant of these proteins had mol wts of 75,000 (75K) and 65K daltons. Furthermore, two glycosylated polypeptides with mol wts of approx 220K and 230K were precipitated by antisera to p30 or p12, but not by antiserum to the major envelope glycoproteins gp69 and gp71. Glycosamine labeling and lectin binding suggested that the 75K-dalton internal core polypeptide is slowly processed to form a 93K-dalton protein. The 65K-dalton protein appeared to be an immediate precursor of the virion core proteins. The processing of this protein could involve intermediates containing p30 and p12 antigens with mol wts of 50K and 40K; however, the latter did not appear to be an obligatory intermediate. Detection of the 40K-dalton protein suggested that the genes for p30 and p12 are adjacent on the genome. These findings suggest that there are several pathways of synthesis and posttranslational processing of polypeptide precursors to the gag proteins and that several of these polypeptides are glycosylated. Different pathways are favored depending on whether the cells are rapidly growing, slowly growing, or stationary. Thus, there are at least two 90K-dalton glycoproteins that appear to be precursors to gp69/71. (24 refs.)

- 78-0861 The Tumor Dormant State.** (Eng) Wheelock, M. F. (Dept. Microbiology, Jefferson Medical College, Thomas Jefferson Univ., Philadelphia, PA 19107); Goldstein, L. T.; Weinhold, K. J.; Carney, W. P.; Marx, P. A. In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapeutic Approaches*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lippman, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 105-116; 1977.



ee experimental murine models of tumor dormancy, each representing a different host response to neoplasia, are described. In the first, Friend leukemia virus (FLV) infection of DBA/2 mice, stimulation of a nonspecific host defense such as interferon by chlorite oxidized oxyamylose-statolon treatment was not sufficient for virus suppression. Restoration of immunocompetence directed against virus-coded antigens was the essential factor for establishing dormancy. The presence of antibody to virion polypeptide p12 in the sera of leukemia mice and its presence in FLV-dormant mice suggest that the humoral immune response to p12 may determine whether or not an FLV-infected mouse develops dormant or overt erythroleukemia. In the second model, female DBA/2 (syngeneic) mice were immunized by ip injection of  $10 \times 10^4$  mitomycin C-treated L5178Y lymphoma cells 5 days prior to injection of  $5 \times 10^4$  live tumor cells. Immunization rendered the mice resistant to subsequent tumor challenge for 55 days (vs 15 days for non-immunized mice). However, the rapid outgrowth of tumor cells from cultures of peritoneal or spleen cells from tumor-dormant mice indicates that factors operative in vivo suppression are lost when these cells are removed from the host. The hybrid effect was investigated in the third model: DBA/2-derived L5178 lymphoma cells were injected into both DBA/2 and BDF<sub>1</sub> mice. BDF<sub>1</sub> mice, but not DBA/2, delayed tumor cell outgrowth and, in some instances, maintained a tumor-dormant state for considerable periods of time. An adherent peritoneal cell with macrophagelike properties may be involved in maintaining dormancy. (20 refs.)

0862 **Effect of Interferon on Exogenous Murine Leukemia Virus Infection.** (Eng) Aboud, M. (Dept. of Microbiology, Bar-Ilan Univ., Ramat-Gan, Israel); Shoor, R.; Berg, S. *Virology* 84(1): 134-141; 1978.

When NIH/3T3 cells were treated with interferon (IF: at a concentration resulting in a 50% reduction of reverse transcriptase activity) before infection with Moloney murine leukemia virus (M-MLV: 1 plaque-forming unit/cell), no significant release of viral progeny occurred as long as IF remained in the medium. This was not due to inhibition of virus replication or to interference with virus penetration, since M-MLV release returned to control levels when IF was removed prior to or 6 hr after infection. Furthermore, IF had no effect on the formation of infectious centers. IF reduced viral RNA synthesis, as did the protein synthesis inhibitor cycloheximide ( $1 \mu\text{g/ml}$ ) when it was added early after infection. When added for 5-9 hr postinfection, the drug had no effect on RNA synthesis. When IF was eliminated from pretreated cultures up to 10 hr before M-MLV infection, progeny release was still affected. These results demonstrate that IF exerts its effect at the early stage of exogenous MLV infection. (30 refs.)

78-0863 **Preliminary Characterization of a Temperature-sensitive Mutant of Moloney Murine Leukemia Virus That Produces Particles at the Restrictive Temperature.** (Eng) Wong, P. K. (Dept. Microbiology, Univ. Illinois, Urbana, IL 61801); Gallick, G. E. *J Virol* 25(1): 187-192; 1978.

A new, spontaneous, temperature-sensitive mutant of Moloney murine leukemia virus, designated *ts7*, was isolated and characterized. The infectivity of *ts7*, determined by a focus-forming-unit assay, was at least 100-times less at the nonpermissive (39 C) than at the permissive (34 C) temperature. The supernatant from *ts7*-infected cells grown at 39 C showed significant infectivity when assayed at 34 C; only small reductions in reverse transcriptase activity and fusion ability were observed upon comparison with the supernatant from 34 C *ts7*-infected cultures. Transmission electron microscopy revealed the presence of virus particles in the supernatant of *ts7*-infected cells at 39 C and in the intercellular spaces of pelleted thin cell sections. *ts7* harvested at 34 C was extremely heat-labile. When incubated at 39 C, this virus has a half-life one-sixth that of the same virus incubated at 34 C or that of wild-type virus at either temperature. The heat lability of the exogenous DNA polymerase activities of *ts7* and wild-type virus was similar. The results suggest that the phenotypic properties of *ts7* are unlike those of any other RNA tumor virus *ts* mutant previously reported. This may be due to its heat lability at the nonpermissive temperature. The results also suggest that the defective function of *ts7* affects the stability of completed virions more than actual virus production. (20 refs.)

78-0864 **A Replication-defective Variant of Moloney Murine Leukemia Virus. I. Biological Characterization.** (Eng) Rein, A. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014); Gerwin, B. I.; Bassin, R. H.; Schwarm, L.; Schidlovsky, G. *J Virol* 25(1): 146-156; 1978.

A clone (8A) isolated from a culture of murine sarcoma virus (MSV)-transformed mouse cells after superinfection with Moloney murine leukemia virus (MuLV-M) produced high levels of C-type virus particles, but only a low titer of infectious MSV and almost no infectious MuLV. When fresh cultures of mouse cells were infected with undiluted clone 8A culture fluids, they released no progeny virus for several weeks after which fully infectious MuLV was produced. Tests of viral host range and of base sequence homology with standard virus isolates did not detect any differences between the progeny isolates of MuLV-8A and MuLV-M itself. It is proposed that clone 8A is infected with a replication-defective variant of MuLV-M and that several weeks after infection of fresh cells, the defect in the viral genome is corrected by back-mutation or by recombination with endogenous viral genomes, resulting in fully infectious progeny MuLV. The progeny MuLV's that arose in two experiments were genetically different from each other, which is consistent



ent with the hypothesis that the progeny virus is formed as the result of an independent genetic event. DNA was isolated from clone 8A cells and assayed for infectivity. No MuLV was produced by cells treated with this DNA, indicating that clone 8A cells do not contain a normal MuLV provirus. (54 refs.)

- 78-0865 Murine Leukemia Virus Infectious Centers Are Dependent on the Rate of Virus Production by Infected Cells.** (Eng) Chesebro, B. (U.S. Dept. Health, Education, and Welfare, Public Health Service, NIH, Natl. Inst. Allergy and Infectious Diseases, Rocky Mountain Lab., Hamilton, MT, 59840); Wehrly, K.; Watson, K.; Chesebro, K. *Virology* 84(1): 222-226; 1978.

Nine murine leukemia cell lines were used to analyze a murine leukemia virus S+ L- (sarcoma-positive, leukemia-negative) infectious center (IC) assay. The rate of virus production was determined by the equilibrium and cell-washing methods and then compared with the observed incidence of IC's for each cell line to define the exact nature of an IC. The results show that detection of virus-producing cells in the IC assay depends on the rate of virus production by individual cells. Although 100% of high-virus-producer cells gave positive IC plaques, only 0.01%-1% of low virus producers were detectable. The findings are in approx agreement with the prediction that a virus producer cell is an IC if it secretes 1 plaque-forming unit of virus within 48 hr of seeding onto the target cell culture. (10 refs)

- 78-0866 Independence of Differentiation Induced by Dexamethasone and Reverse Transcriptase Activity in Mouse Myeloid Leukemic Cells.** (Eng) Kasukabe, T. (Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Saitama 362, Japan); Honma, Y.; Okabe, J.; Hozumi, M. *Cancer Lett* 3(5/6): 333-337; 1977.

The effect of  $1 \times 10^{-6}$  M dexamethasone (DM) on the M1 clone of 34Y cells from a spontaneous myeloid leukemia of an SL mouse was investigated. This treatment increased the phagocytic activity of the cells and induced their locomotive activity in soft agar. In contrast to previous studies, reverse transcriptase (RT) activity was not affected. DM did, however, stimulate RT activity in a nonproducer clone of Kirsten murine sarcoma virus-transformed BALB/3T3 cells pretreated with  $1.1 \times 10^{-4}$  M 5-iododeoxyuridine. DM did not significantly induce increased amounts of poly(rC)-oligo(dG)-directed RT activity in the virus fraction from M1 cells in the presence of labeled deoxyguanosine triphosphate. DM significantly inhibited the growth of these cells by 48 hr, but no increase in RT activity per cell was noted until max phagocytic activity was reached. RT activity

in virus pellets of DM-treated cells was the same as that in untreated cells. It is suggested that differences between these findings and those of a previous study are due to clonal differences. (12 refs)

- 78-0867 Physical Map of the Kirsten Sarcoma Virus Genome as Determined by Fingerprinting RNase T1-resistant Oligonucleotides.** (Eng) Shih, T. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014); Young, H. A.; Coffin, J. M.; Scolnick, E. M. *J Virol* 25(2): 238-252; 1978.

A physical map of the Kirsten sarcoma virus genome was deduced from an analysis of its large RNase T1-resistant oligonucleotides. Kirsten murine leukemia virus (Ki-MuLV) sequences were detected in T1 oligonucleotides at the 3' end immediately next to the poly(A) termini of RNA molecules and extended 1,000 nucleotides into the genome. The rat genetic sequences extended from this distance all the way to the 5' termini of Ki-SV RNA molecules, where a small stretch of the Ki-MuLV sequence was detected. Comparison of the fingerprints of Ki-SV RNA and the RNA of the endogenous rat sarcoma virus genetic sequences indicated that > 50% of the T1 oligonucleotides were similar between Ki-SV and the endogenous rat sarcoma RNA, suggesting an identical primary nucleotide sequence in 50% of the viral genome. The results indicate that Ki-SV arose by recombination between the 5' and 3' ends of Ki-MuLV and a large portion of the homologous sequences of the endogenous rat sarcoma virus RNA. Although the endogenous rat sarcoma virus is not readily transmissible to most host cells, acquisition of Ki-MuLV termini within the Ki-SV genome may enable Ki-SV to be replicated readily in a variety of host cells with the aid of helper C-type viruses. (28 refs.)

- 78-0868 Properties of a Transforming Virus, KiMSV(RHHV), Isolated from a Co-culture of Rat HTC-H1 Cells with K-NRK Cells.** (Eng) Yang, S. (Lab. Cell Biology, NCI, Bethesda, MD, 20014); Malech, L.; Wu, R. S.; Woronow, D. I. *J Gen Virol* 38(2): 209-219; 1978.

The morphological, biological, immunological, and chemical characteristics of KiMSV(RHHV), a rat helper virus pseudotype Kirsten sarcoma virus isolated from infected Fischer rat embryonic cells, were determined. The virus has a C-type virus ultrastructure, is strictly rat-tropic, and is able to transform rat cells in vitro. Antigenically, KiMSV(RHHV) demonstrates cross-reactivity with antiserum specific against rat leukemia virus, no cross-reactivity with antiserum against Moloney leukemia virus, and only minor cross-reactivity with antiserum against cat leukemia virus. (12 refs.)



s. Analysis of virus proteins and glycoproteins by equilibrium acrylamide gradient gel electrophoresis showed that the complex possesses both a gp70 fraction and a p30 fraction. The virus sediments isopycnicly in a linear sucrose gradient at 1.145-1.155 g/ml and possesses RNA and reverse transcriptase activity. (28 refs.)

869 **Infection, Replication and Transformation of Cells by a 'Hamster Sarcoma Virus' (Meeting Abstract).** (Eng) Jerabek, L. B. (Cornell Univ. Medical Coll., Ithaca, NY). *Diss Abstr Int [B]* 38(5): 2044B; 1977. (no refs.)

870 **Characteristics of Lymphomas in the BALB/cfRIII Mouse Strain.** (Eng) Squartini, F. (Laboratory of Experimental Oncology, Istituto di Anatomia Patologica, Università, Pisa, Italy); Urbano, U. *Tumori* 63(5): 437-448; 1977.

Characteristics of 392 lymphomas in 1,607 BALB/cfRIII mice from  $F_0$  to  $F_4$ , are reviewed. Lymphoma incidence increased rapidly in the first five generations, reached a plateau in  $F_6$  to  $F_{20}$  (350 lymphomas from  $F_0$  to  $F_{20}$ ), and then decreased slowly until it disappeared. After  $F_{35}$ , only sporadic cases of lymphoma were observed. The frequency of lymphomas was greater in the offspring of parents that developed lymphomas than in those of lymphoma-free parents. Three main types of lymphomas were recognized on the basis of gross morphology, histology, and age: (1) early, lymphocytic, with thymic involvement; (2) early, lymphocytic, without thymic involvement; and (3) late, histiocytic, without thymic involvement. The first two types are virus-induced and thymus-dependent, the third is both virus- and thymus-independent. Types 1 and 3 increased with the generations. It is suggested that the leukemia virus was milk-transmitted in BALB/cfRIII mice from parent to offspring, but that it had been introduced by milk from the RIII foster mother. The mechanisms responsible for activation of a latent RIII leukemia virus soon after its induction into BALB/c mice by foster nursing and the appearance or inactivation of this virus after 30 generations of inbreeding are not known. (23 refs.)

871 **Protein Composition and Immunologic Properties of C-Type Oncornavirus from Spontaneous Phosphoroma of CC57Br Mice (OP Virus).** (Rus) Zaretzki, I. Z. (D. I. Ivanovskii Inst. Virology, Acad. Medical Sciences USSR, Moscow, USSR); Lovenetskii, A. N.; Bogovskii, B. P.; Irlin, I. S.; Kiselev, F. L. *Vopr Virusol* (3): 354-359; 1977.

skii, B. P.; Irlin, I. S.; Kiselev, F. L. *Vopr Virusol* (3): 354-359; 1977.

The protein composition and immunological properties of the C-type oncornavirus (OP virus) from spontaneous lymphosarcomas of CC57Br mice were studied. Up to 17 polypeptides were found, with the major ones being identified as p100, p125, p72, p31, p21, p16, and p13. The protein composition was similar to that of other C-type murine oncornaviruses. The virus contained a group-specific gs-1 antigenic determinant associated with p31. In terms of its type-specific reactivity, OP virus belongs to the antigenic subgroup of Gross leukemia virus. (16 refs.)

78-0872 **C-Type Virus Protein p30 in Blood from Inbred Mice Correlates with Their Later Incidence of Leukemia.** (Eng) Nexø, B. A. (Fibiger Lab., DK-2100 Copenhagen O, Denmark); Krog, H. H. *Infect Immun* 15(2): 376-381; 1977.

The major core protein of mouse C-type viruses, p30, was measured in the spleen, thymus, and blood of mice from strains differing in their incidences of spontaneous lymphoreticuloendothelial malignancies. The p30 concentrations in the spleen and thymus had a moderate and weak correlation, respectively, with leukemia incidence. There was a 100-fold difference in blood p30 concentration between AKR and C58 mice (high leukemia strains) and low leukemia strains; variation between individuals, however, was moderate. SJL mice, which develop reticulum cell neoplasms at an age and frequency similar to those of leukemic AKR and C58 mice, demonstrated a variability of values; it is unknown if this variability is related to the different disease. In AKR mice, p30 concentrations rose shortly after birth and reached their final values within the first 3 wk of life. In DBA/2 mice, the concentration declined slightly in the first month and stayed low for 3 mo; conversion to high blood p30 occurred sporadically at older ages. In strain 129 mice, p30 blood concentrations were low, regardless of age. Most of the p30 in the blood of AKR mice was found in the RBC fraction, some was found in the WBC fraction, but only very little was found in the plasma. However, the virion content per cell was higher in the WBC (several hundred virions/WBC) than in the RBC (< 1 virion/RBC). (31 refs.)

78-0873 **Increased Immunogenicity of Low-antigenic Rat Tumors after Superinfection with Endogenous Murine C-type Virus in Nude Mice.** (Eng) Kozumaki, N. (Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden); Fenyo, E. M.; Giovanella, B. C.; Klein, G. *Int J Cancer* 21(1): 62-66; 1978.



Experiments were performed to determine whether endogenous, xenotropic mouse viruses can augment immunogenicity of low-antigenic rat tumors. Two methylcholanthrene-induced fibrosarcomas in BDIX rats (MBDA) and (MDBD), two ethylnitrosourea-induced neurogenic tumors in BDIX rats (290T and GE3A), and two polyoma virus-induced sarcomas in Wistar-Fu rats (PW31 and PW41) were used. The transformed cells were repeatedly passaged in nude mice following sc injection. Testing of the passaged cells revealed that MBDB and PW41 reacted with antisera to gp71, p30, and p12 viral antigens, indicating superinfection with endogenous mouse virus (EMV). Attempts to superinfect 290T and GE3A with supernatant of the infected PW41 culture resulted in infection of 290T only. When inoculated sc into untreated syngeneic rats, three EBV-infected rat tumors (EMV-MBDB, EMV-290T, and EMV-PW41) showed significantly reduced transplantability compared with noninfected tumors. EMV-MBDB and EMV-290T were completely rejected at challenge doses 10 to 100 times the LD50, and 5/7 EMV-PW41 were rejected at a dose 5 times the LD50. Syngeneic rats were then immunized three times with irradiated cells; 7 days later they received 400 rads whole body irradiation and were then challenged with the noninfected tumor. Wistar/Fu rats immunized with EMV-PW41 showed no improvement in PW41 rejection. BDIX rats immunized with EMV-290T rejected the respective tumors with no cross-immunity, while rats immunized with irradiated but noninfected tumors showed no significant reaction. Thus, EMV infection augmented the immunogenicity of the rat tumors. (21 refs.)

**78-0874 Identification of a 30S RNA with Properties of a Defective Type C Virus in Murine Cells.** (Eng)

Howk, R. S. (Meloy Lab., Rockville, MD, 20850); Troxler, D. H.; Lowy, D.; Duesberg, P. H.; Scolnick, E. M. *J Virol* 25(1): 15-123; 1978.

A 30S RNA species found in NIH 3T3 and SC-1 cells was characterized. Hybridization experiments indicated that it had little homology to helper-independent murine C-type viruses; however, pseudotyping revealed that the 30S species found in NIH clone 4 is C-type viral RNA. The 30S RNA is present in 10 to 20 copies per diploid genome in normal mouse DNA, it is inducible to high levels of expression in cells derived from inbred or wild mice, and it is packaged by C-type viruses growing in mouse cells. These properties suggest that it is a defective endogenous murine C-type virus and that it is analogous to a previously described class of defective endogenous rat C-type virus shown to be the progenitor of Kirsten and Harvey murine sarcoma viruses. (33 refs.)

**78-0875 Sequences Associated with Intracisternal A Particles Are Reiterated in the Mouse Genome.** (Eng)

Lueders, K. K. (Lab. Biochemistry, NCI, Bethesda, MD 20014); Kuff, E. L. *Cell* 12(4): 963-972; 1977.

Using labeled complementary DNA (P<sup>h</sup>-cDNA) for R sequences specifically associated with murine intracisternal A-type particles, multiple copies of this information were found in high-mol-wt nuclear DNA of all mice examined [Mus musculus (BALB/c, NIH Swiss, A/Jax, and feral)] (Mus cervicolor). Reiteration frequencies varied from 1,051,800 per haploid genome; fewer copies (450) were found in BALB/3T3 cells. The reiteration frequencies in the DNA of A-particle-rich tumor cells (myeloma and neuroblastoma) were not higher than those in normal tissues. Multiple copies were retained when cellular DNA's were sedimented through alkaline sucrose gradients, indicating that these sequences were integrated in the mouse genome. Hybridization with excess nuclear DNA as well as cDNA indicated a similar proportion (25%-30%) of the 29S RNA to be transcribed from sequences reiterated 1,000-2,000 times. In situ hybridization with cDNA showed that the reiterated sequences were associated with many chromosomes and that they were concentrated over certain regions of some chromosomes. The presence of reiterated sequence transcripts in poly(A) RNA from a neuroblastoma A-particle fraction was confirmed by direct hybridization of the RNA with cellular DNA. These results indicate that the RNA sequences are reiterated in the DNA of both somatic and germ cells and that high copy numbers are not necessarily linked to neoplastic transformation or overt A-particle expression. The high degree of conservation of these sequences suggests that they may serve some essential cellular function. (42 refs.)

**78-0876 Further Study of Spontaneous Viral Production Using Transplantable HEP-2 Cells.** (Rus)

sinksy, T. F. (D. I. Ivanovsky Inst. Virology, Acad. Med. Sciences USSR, Moscow, USSR); Uryvaev, L. V.; Il'in, V.; Zhdanov, V. M. *Vopr Med Khim* 23(6): 824-829; 1977.

Two absorbance maxima were observed at two densities (1.15-1.16 g/ml) when cultured HEP-2 cells were analyzed by sucrose gradient sedimentation following ultracentrifugation. These fractions were tested for the presence of RNA- and DNA-dependent DNA-polymerase. The structures with density 1.15-1.16 g/ml were identified as oncoviruses on the basis of their characteristic buoyant density and the presence of RNA-dependent DNA-polymerase. In the presence of RNA- and DNA-dependent polymerase reaction products and the buoyant density of oncornaviral nucleotides in sucrose and CsCl gradients are presented. The optimal conditions for the reverse transcriptase reaction of D-type viruses are characterized. (17 refs.)

**78-0877 From Deoxynucleotides to DNA Synthesis.** (Eng)

Reichard, P. (Medical Nobel Inst.,



mistry Dept. I, Karolinska Inst., S-104 01 Stockholm, Sweden). *Fed Proc* 37(1): 9-14; 1978.

polyoma DNA replication was used as a model to show that DNA synthesis can be separated into different steps involved in the initiation and elongation processes. The role of ribonucleotide reductase in the regulation of DNA synthesis is also discussed and the relationship between the two processes is compared. (25 refs.)

**78-0878 Comparison of Nuclease Digestion of Polyoma Virus Nucleoprotein Complex and Mouse Chromatin.** (Eng) Ponder, B. A. (Dept. Molecular Virology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London EC2A 3PX, England); Crew, F.; Crawford, L. V. *J Virol* 25(1): 175-186; 1978.

Polyoma virus nucleoprotein complex was isolated from distilled virions and digested with micrococcal nuclease and DNase I, and the results were compared with those of the digestion of chromatin from mouse nuclei. The nucleosome structures (140 base pairs of DNA that are resistant to nuclease digestion and closely associated with histones) were similar, but the spacing of the nucleosomes was irregular in polyoma virus nucleoprotein complexes and regular in mouse chromatin. The average nucleosome repeat length in the complexes was 185 base pairs, which suggests that, unless there are substantial stretches of free DNA, each complex contains 26 nucleosomes. The commonly used method of preparing the nucleoprotein complex by disruption of virions at 10.2 may lead to significant damage to the DNA-histone structure and should probably be abandoned. The results are consistent with a previous conclusion that one superhelical turn in closed circular DNA corresponds to one nucleosome. (24 refs.)

**78-0879 Temperature-sensitive Growth Regulation in One Type of Transformed Rat Cells Induced by tsA Mutant of Polyoma Virus.** (Eng) Seif, R. (Centre de Chimie, Université de Nice, 06034 Nice, France); Cuzin, J. *J Virol* 24(3): 721-728; 1977.

3T3 fibroblast line with a low saturation density was established from Fisher rat embryo cells. After infection with wild-type polyoma virus (PV) or a temperature-sensitive mutant (tsA), transformants were isolated and cloned at 33°C on the basis of their ability to grow as dense foci on plastic in liquid medium (type N) or to form colonies in soft agar (type A). Polyoma T antigen was detected in all of the transformed cells. The following growth characteristics were studied for both types at 33°C and 41°C: saturation density, growth in soft agar and at a low serum concentration, colony-forming ability and generation time. At 33°C, tsA-N transformants behaved similarly to transformed cells, but at 41°C, they

reverted to the nontransformed phenotype. tsA transformants and all the wild-type transformants exhibited the transformed phenotype at both low and high temperatures. These results indicate that PV can induce at least two types of transformed lines. In one, the activity of the protein affected by the tsA mutation appears to be necessary for the expression of several of the characters defining the transformed state. (34 refs.)

**78-0880 Glucocorticoids Induce Focus Formation and Increase Sarcoma Viral Expression in a Mink Cell Line That Contains a Murine Sarcoma Viral Genome.** (Eng) Lowy, D. R. (Dermatology Branch, NCI, Bethesda, MD 20014); Scolnick, E. M. *J Virol* 25(1): 157-163; 1978.

Dexamethasone ( $3 \times 10^{-10}$  -  $3 \times 10^{-6}$  M) induced foci of morphologically transformed cells in a small proportion of a mink cell line that contains the Moloney murine sarcoma viral genome (S+L-). The dexamethasone-induced foci closely resembled those induced by RD-114 virus. The induction was glucocorticoid-specific, since other steroids with glucocorticoid activity (prednisolone, cortisol, and aldosterone) induced foci with an efficiency that paralleled their glucocorticoid activity, but steroids lacking glucocorticoid activity (17 $\beta$ -estradiol, testosterone, and progesterone) did not induce foci. The foci contained increased amounts of sarcoma viral antigen, as determined by immunofluorescence, and the treated cultures had increased levels of viral p30 antigen and sarcoma-specific viral RNA. The continued presence of glucocorticoid was required for maintenance of the foci and for the enhanced expression of the sarcoma viral genome. These studies establish that glucocorticoids can affect the intracellular levels of a C-type viral genome. (24 refs.)

**78-0881 Isolation and Characterization of an Endogenous Type C RNA Virus of Mink (Mv1Lu) Cells.** (Eng) Barbacid, M. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Tronick, S. R.; Aaronson, S. A. *J Virol* 25(1): 129-137; 1978.

A reverse transcriptase-containing virus, which was released spontaneously from Mv1Lu mink cells after long-term passage in tissue culture, was characterized. Molecular hybridization showed that the DNA of normal mink cells possessed extensive nucleotide sequence homology with a reverse-transcription product of the viral genome, demonstrating that the new isolate was an endogenous virus. The virus cross-reacted in a broad interspecies immunoassay that detects shared antigenic determinants of the major structural proteins of mammalian C-type viruses. However, its lack of immunological identity with the major structural protein, p30, of other mammalian C-type viruses and the unique antigenic determinants of its p30, as defined in a homologous radioim-



munoassay developed for this protein, established the mink virus as a new C-type virus isolate. Heterologous radioimmunoassays demonstrated that this virus, although clearly distinct, is more closely related to the W/Fu strain of rat leukemia virus (RaLV) and the Rickard strain of feline leukemia virus (FeLV) than to the other mammalian C-type viruses (mouse, monkey, baboon) tested. The fact that mink cells can remain non-virus-producing for many cell generations suggests that there normally exists some cellular restriction to endogenous virus expression. (51 refs.)

- 78-0882 Increased Susceptibility to Feline Leukemia Virus Infection in Cats Exposed to Methylnitrosourea.** (Eng) Schaller, J. P. (Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH, 43210); Mathes, L. E.; Hoover, E. A.; Koestner, A.; Olsen, R. G. *Cancer Res* 38(4): 996-998; 1978.

The effect of methylnitrosourea (MNU) on the susceptibility of specific-pathogen-free cats to feline leukemia virus (FeLV) was determined. Cats received either 5, 10, or 20 mg/kg MNU iv; the Rickard strain of FeLV (1-2 ml thymic tumor homogenate containing  $5 \times 10^3$  focus-forming units/ml, ip); FeLV + 15 mg/kg MNU; or FeLV + 20 mg/kg MNU. At 20 mg/kg MNU, peripheral blood WBC were depressed within 3 days of administration, segmented neutrophils were depressed to within 8% of initial values within the first 2 wk, lymphocyte populations were depressed 30%-50%, and Hb and hematocrit levels were depressed 25%. Less-severe or negligible changes in these parameters were induced at the lower doses. Similar effects were observed in cats receiving FeLV + 15 or 20 mg/kg MNU. A >70% reduction in circulating WBC's was noted between days 4-14, and segmented neutrophils were reduced to <90% of preinoculation levels. No leukopenia was observed in cats receiving FeLV alone. By 4 wk postinjection, 6/9 MNU + FeLV cats developed evidence of viremia, compared with only 2/12 cats given FeLV alone, and 3 of the former, but none of the latter, had developed the viremia by 2 wk. It is suggested that exposure of cats to MNU increases their susceptibility to FeLV infection. (16 refs)

- 78-0883 Endogenous Feline (RD-114) and Baboon Type C Viruses Have Related Specific RNA-binding Proteins and Genome Binding Sites.** (Eng) Sen, A. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Sherr, C. J.; Todaro, G. J. *Virology* 84(1): 99-107; 1978.

Binding between the major phosphoproteins (p16) and the genomic RNA's of endogenous baboon and feline C-type viruses was studied. The p16 from *Felis catus* (RD-114 virus), *Papio papio* (PP-1 virus), and *Papio cynocephalus* (M28 and M7 virus) bound to viral RNA's purified from these viruses but not to RNA's from Rauscher murine leukemia virus,

S2CL3 virus, or Rous sarcoma virus. These findings indicate that the specific RNA-binding function of the viral phosphoproteins and their binding sites of viral RNA genomes have been evolutionarily conserved, even though the baboon and cat C-type viruses have been genetically transmitted in different mammalian orders. (25 refs)

- 78-0884 A Comparison of Cat and Rat Cultures for Assay of Woolly Monkey Sarcoma and Related Viruses.** (Eng) Sarma, P. S. (NCI, Bethesda, MD 20014); Law, M. J. *Proc Soc Exp Biol Med* 156(3): 480-484; 1977.

The ability of rat embryo fibroblasts from Osborne-Mendel and Fischer rats to propagate woolly monkey sarcoma virus (WMSV) was compared with that of feline embryo fibroblasts of lines K-655, D843, and H927. WMSV caused morphological transformation of cat cells at dilutions ranging from  $10^{-1}$  to  $10^{-4}$ . Rat cells produced cell transformation only at dilutions up to  $10^{-1}$ . Similar observations were found with the HL-23 strain of primate type C virus. Furthermore, cat cells were at least as sensitive as rat cells to productive infection by nontransforming woolly monkey-associated virus and HL-23. Feline culture inoculates with WMSV passaged in rat culture showed similar transformation effects to those observed in feline cultures inoculated directly with WMSV. A comparison of three cat cell cultures indicated minor variations in their relative susceptibilities to replication and formation with viruses. Strains D843 and I-655 appeared to be more sensitive than strain H927. Thus cat embryo cells are superior to rat embryo cells for in vitro assay of transforming and nontransforming primate type C RNA viruses. (19 refs.)

- 78-0885 Complement-mediated Lysis of Type-C Virus Effect of Primate and Human Sera on Various Retroviruses.** (Eng) Sherwin, S. A. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Benveniste, R.; Todaro, G. J. *Int J Cancer* 21(1): 6-11; 1978.

The ability of human and other primate sera to lyse C-type RNA tumor viruses was measured using the reverse transcriptase-release assay. The viruses used included Rauscher murine leukemia virus, M28 (endogenous to baboons), S2CL3 (woolly monkey virus), and Mason-Pfizer monkey virus (type C). Both normal and leukemic human sera, as well as sera from several other primate species (apes, Old World monkeys, and New World monkeys), were capable of lysing endogenous and infectious primate and murine-C type viruses. Cat and rabbit sera also possessed this activity. Each serum with complement-mediated virolytic activity lysed several classes against which it was tested. Primate species that simultaneously release retroviruses, such as baboons and squirrel monkeys, and those that are infected with exogenous



viruses, such as rhesus monkeys and gibbon apes, all lysed their respective viruses. The efficiency of viral lysis correlated better with primate phylogeny than C-type virus release or transmission. Heating destroyed the virolytic activity. Thus, complement-mediated viral lysis does not play a role in blocking the release or transmission of C-type viruses among primates. (17 refs.)

0886 **Characterization of a Fetal Calf Serum-derived Molecule Reactive with Human Natural Antibodies: Its Occurrence in Tissue Culture-grown Type C NA Viruses.** (Eng) Snyder, H. W. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Fox, M. *Immunol* 120(2): 646-651; 1978.

A fetal calf serum (FCS) molecule that binds to virus from culture fluids and that shows only partial absorption of radioimmunoprecipitation (RIP) reactivity was characterized. This assay indicated that a simian sarcoma virus-simian sarcoma-associated virus, purified from culture fluids of infected normal rat kidney cells, acquires a surface antigen from serum used in the tissue culture medium. This antigen, which can be acquired from FCS or horse, swine, rabbit, or chicken serum, accounted for most of the precipitating activity exhibited by natural human antibodies for membrane-associated antigens of these viruses. The estimated mol wt of this protein is approx 55,000-60,000 daltons. It has been identified as a minor constituent of FCS (<0.1% of total protein), and has the antigenic capacity of whole FCS. It is suggested that this protein is selectively absorbed from FCS by cells in culture and then picked up by the virions during budding. (9 refs.)

0887 **Cleavage and Ligation of Simian Adenovirus 7 DNA by Restrictive Eco RI Endonuclease and DNA Ligase.** (Rus) Kislina, O. S. (D. I. Ivanovsky Inst. of Virology, Moscow, USSR); Naroditsky, B. S.; Chaplygina, M.; Karamov, E. V.; Tikhonenko, T. I.; Dreizin, R. S.; Lotarskaya, E. V.; Andrianov, V. M.; Vinetsky, Yu. P. *Vopr Virolog* (3): 271-274; 1977.

To determine the optimal conditions for simian adenovirus (SA7) DNA cleavage and ligation, DNA extracted from SA7 was exposed to Eco RI restrictase, and the resulting DNA fragments were then treated with DNA ligase. Agarose electrophoresis of the Eco RI-treated material produced two bands which corresponded to DNA fragments with molecular wts of  $10.8 \times 10^6$  and  $12.4 \times 10^6$ , respectively (native DNA was seen as single band). After ligation with DNA ligase, three bands resulted: two corresponded to the DNA fragments, one to the native DNA molecule. Densitometric estimation of the fraction of ligated DNA molecules showed that approx 30% of the original fragment mixture underwent ligation. (9 refs.)

78-0888 **Herpesvirus ateles DNA and Its Homology with Herpes-virus saimiri Nucleic Acid.** (Eng) Fleckenstein, B. (Institut für Klinische Virologie der Universität Erlangen-Nürnberg, 8520 Erlangen, W. Germany); Bornkamm, G. W.; Mulder, C.; Werner, F. J.; Daniel, M. D.; Falk, L. A.; Delius, H. *J Virol* 25(1): 361-373; 1978.

The structure of *Herpesvirus ateles* DNA was investigated and compared with that of *H. saimiri*. Analytical centrifugation and partial denaturation indicated that two types of *H. ateles* DNA molecules are encapsidated: (1) M genomes, which contain 74% light sequences (L-DNA, 38% guanine + cytosine) and 26% highly repetitive sequences (H-DNA, 75% guanine + cytosine) and (2) defective H genomes, which consist exclusively of repetitive H-DNA. M genomes consist of an L-DNA region of  $70 \times 10^6$  daltons inserted between H-DNA termini of variable length. They have a shorter H-DNA at one end of the molecule and a long stretch of H-DNA at the other end and an av mol wt of  $89.8 \pm 8.5 \times 10^6$  daltons. Thus, they resemble the M genomes of *H. saimiri*. The H-DNA of two independent *H. ateles* isolates, strains 810 and 73, had different cleavage patterns with restriction endonuclease *Sma* I. The strain 73 H-DNA repeat unit was shorter (930,000 mol wt) than that of strain 810 H-DNA (1,035,000). Corresponding DNA sequences of the two strains were completely homologous in cross-hybridizations, but a discrete nucleotide sequence divergence was detected by melting temperature ( $T_m$ ) measurement of DNA hybrid molecules. Hybridization of L-DNA from *H. ateles* with L-DNA from *H. saimiri* showed a 35% homology between the respective sequences;  $T_m$  measurements indicated a 9% mismatching in cross-hybridizing parts of the L regions. There was little homology between the H-DNA of *H. ateles* and *H. saimiri*. However, the viruses probably evolved from a common ancestor. (35 refs.)

78-0889 **Transformation of Squirrel Monkey Lymphocytes by Epstein-Barr Virus: Effect of Donor Age.** (Eng) Ablashi, D. V. (Viral Oncology Program, NCI, Bethesda, MD, 20014); Easton, J. M.; Pearson, G. R. *Cancer Lett* 3(5/6): 319-324; 1977.

The ability of Epstein-Barr virus (EBV) from B95-8 cells to transform lymphocytes from juvenile and adult squirrel monkeys (*Saimiri sciureus*) was investigated. All monkeys except the seven adults aged 2-3 yr were checked and found to be free of *Herpesvirus saimiri* infection. The lymphocytes were incubated with  $1.0 \times 10^6$  transforming units of virus. Lymphocytes from the 16 juvenile monkeys were transformed in 15-30 days. Only 4/7 adults aged 2-3 yr had transformable lymphocytes (14-21 days), and only 2/4 adults aged 2.5-5 yr had transformable lymphocytes (35-50 days). In human studies, lymphocytes from two neonates transformed in 12 and 14 days, but those from two seronegative adults transformed in 37 and 39 days. All simian and human transformed cells were of B derivation, contained Epstein-Barr nuclear antigen, formed colonies in soft agar, and produced S antigen. It is



not known whether the transformed cells produced EBV. Transformed cells from monkeys aged 2-3 yr produced low levels of early antigen. Cells refractory to transformation contained no detectable amounts of nuclear or S antigen after incubation. (14 refs)

- 78-0890 Cytofluorometry of Lymphocytes Infected with Epstein-Barr Virus: Effect of Phosphonoacetic Acid on Nucleic Acid.** (Eng) Lemon, S. M. (Dept. Virus Diseases, Walter Reed Army Inst. Res., Walter Reed Army Medical Center, Washington, DC 20012); Hutt, L. M.; Pagano, J. S. *J Virol* 25(1): 138-145; 1978.

The effect of phosphonoacetic acid (PAA) on DNA synthesis in Epstein-Barr virus (EBV)-infected lymphocytes was investigated. PAA (200  $\mu\text{g}/\text{ml}$ ) inhibited  $^3\text{H}$ -thymidine incorporation by human umbilical cord lymphocytes infected with EBV strain P94 but not the incorporation by mitogen-stimulated cells. Transformed cell lines did not develop from infected cord cell cultures treated with 100  $\mu\text{g}/\text{ml}$  PAA. Cytofluorometric analysis showed marked increases in cellular nucleic acid (RNA and DNA) content as early as 9 days after infection of cord cells in the absence of PAA and before any significant enhancement of  $^3\text{H}$ -thymidine incorporation. EBV led to increases in cellular nucleic acid even when 200  $\mu\text{g}/\text{ml}$  PAA was added to the cell cultures before infection. These apparently contradictory results suggest that EBV induces fundamental alterations in the control of lymphocyte nucleic acid synthesis or cell division without prior replication of viral DNA by the virus-induced DNA polymerases. (26 refs.)

- 78-0891 Epstein-Barr Virus (EBV) Receptors, Complement Receptors, and EBV Infectibility of Different Lymphocyte Fractions of Human Peripheral Blood: I. Complement Receptor Distribution and Complement Binding by Separated Lymphocyte Subpopulations.** (Eng) Yefenof, E. (Dept. Tumor Biology, Karolinska Institutet S104 01 Stockholm 60, Sweden); Bakacs, T.; Einhorn, L.; Ernberg, I.; Klein, G. *Cell Immunol* 35(1): 34-42; 1978.

Human peripheral lymphocytes were fractionated into a number of B-, T-, and O-cell fractions and characterized with regard to several surface receptors. There was a strong correlation between the frequency of erythrocyte-antibody complement (EAC) receptor-positive cells and the percentage of complement membrane fluorescence (CMF)-stained cells following exposure of the cells to fresh human serum and subsequent staining with an anti-C3 conjugate. CMF staining did not diminish in C4-deficient or hypogammaglobulinemic serum or in the presence of EDTA or ethyleneglycoltetraacetic acid- $\text{Mg}^{2+}$  (EGTA- $\text{Mg}^{2+}$ ), but it was completely negative with C3-depleted normal human serum. The staining is therefore most likely due to the direct binding of C3

to preformed receptors on the lymphocyte surface. The correlation between EAC rosetting and CMF suggests that this binding occurs via the same receptors that bind the activated C3 in the EAC complex. C3 receptors were also detected on surface immunoglobulin-positive B-cell fractions on part of the O-cell population, and on some of the Fc receptor-positive T cells. (20 refs.)

- 78-0892 Epstein-Barr Virus (EBV) Receptors, Complement Receptors, and EBV Infectibility of Different Lymphocyte Fractions of Human Peripheral Blood: II. Epstein-Barr Virus Studies.** (Eng) Einhorn, L. (Dept. Tumor Biology, Karolinska Institutet S 104 01 Stockholm Sweden); Steinitz, M.; Yefenof, E.; Ernberg, I.; Bakacs, T.; Klein, G. *Cell Immunol* 35(1): 43-58; 1978.

The ability of various lymphocyte fractions of human peripheral blood to adsorb infectious Epstein-Barr virus (EBV) and to respond to EBV infection by EBV-determined nucleic acid (EBNA) synthesis and by cellular DNA synthesis was investigated. In B-cell fractions, the frequency of surface immunoglobulin (Ig)-positive and of complement receptor positive (CRP) cells showed a good correlation with the frequency of EBV-binding cells. There was a close relationship among surface Ig-positive, CRP, and EBV-binding cells, frequency of EBNA-positive cells 2-3 days after infection and stimulation of cellular DNA synthesis. The O-cell fractions remaining after the removal of nylon adherent and erythrocyte rosetting cells contained a certain frequency of CRP cells and absorbed EBV to a limited extent, but they did not respond to EBV infection with EBNA induction or stimulation of DNA synthesis. None of the T-cell fractions absorbed EBV, including the fraction that contained some CRP cells. It is concluded that the previously demonstrated relationship between EBV receptors and complement receptors on lymphoblastoid lines also holds for peripheral B lymphocytes. The EBV receptor of the B cell is functionally active, because EBV binding was regularly followed by the induction of EBNA and of DNA synthesis in the B target cells. O cells, which carry complement receptors and absorb EBV to a certain extent, do not respond with EBNA synthesis or DNA stimulation, probably as a result of intracellular restrictions. (19 refs.)

- 78-0893 Serum IgA Antibodies to Epstein-Barr Virus Capsid Antigen Preceding Symptoms of Nasopharyngeal Carcinoma (Letter to Editor).** (Eng) Ho, F. (Medical and Health Dept., Inst. Radiology and Oncology, Queen Elizabeth Hosp., Kowloon, Hong Kong); Kwok, C.; Ng, M. H.; de-The, G. *Lancet* i(8061): 436; 1978.

Epstein-Barr virus (EBV)-specific IgA antibodies constitute a sensitive marker for the diagnosis of clinical and subclinical nasopharyngeal carcinoma (NPC) and, possibly, for identifying



those at risk of the disease. Three additional NPC patients whom symptomatic serum specimens were available are reported. Two had definite serum IgA anti-virus capsid anti-VCA reactivity 30 and 35 mo before the appearance of symptoms. The titers did not change appreciably with disease evolution. Serum was available from the third patient and 55 mo before symptoms appeared. Although he had an IgA anti-VCA titer of 80 2 mo after the diagnosis of NPC, a titer of 5 in the presymptomatic sera was considered insufficient to suggest occult NPC. The results suggest that IgA anti-VCA is present long before the onset of NPC and that it could be used as a preclinical and epidemiological marker for NPC. (10 refs)

**78-0894 Congenital Infection with Cytomegalovirus and Epstein-Barr Virus.** (Eng) Joncas, J. H. (Dept. Microbiology, Hopital Sainte-Justine, 3155 chemin Cote Ste-Catherine, Montreal, PQ H3T 1C5, Canada); Wills, M.; McLaughlin, B. *Can Med Assoc J* 117(12): 1417-1418; 1977.

A case of congenital cytomegalovirus (CMV) infection associated with congenital or early neonatal Epstein-Barr virus (EBV) infection is reported. Serum samples taken from the mother and from the infant at birth and age 3 mo contained high titers of CMV and EBV IgG antibodies. IgM antibodies were also found in the paired sera tested at 3 and 9 mo. At birth, the IgG titers against the CMV and EBV capsid antigens were lower in the infant's serum than in the maternal serum, which suggested congenital viral infection. (10 refs.)

**78-0895 The Interrelationship Between Human Cytomegalovirus and Host Cell DNA Synthesis** (Meeting Abstract). (Eng) Hutt, E. R. (Pennsylvania State Univ., PA). *Diss Abstr Int* 17(5): 2043B; 1977. (no refs.)

**78-0896 Effect of Vaccinia Virus and Herpes Simplex Viruses Type 1 and 2, on the Chromosomal System of Human Lymphocytes, in Cultures In Vitro.** (Eng) Blazynski, F. (Dept. Microbiology and Epidemiology of Quarantine Diseases, Inst. Maritime and Tropical Medicine, Gdynia, Poland); Towianska, A.; Dabrowski, J.; Kubica, B. *Bull Inst Trop Med Gdynia* 28(3/4): 209-214; 1977.

The effects of WR strain vaccinia virus, H/V strain herpes simplex virus type 1 (HSV-1), and EG strain HSV-2 on chromosomes from in vitro cultures of human peripheral lymphocytes were determined. In the first group of uninfected lymphocytes, chromosomal aberrations amounted to 9% (ie, 4.5% chromatid gaps and 4.5% chromatid breaks). Lymphocytes from the same patients infected with vaccinia virus had 46% aberrations/cell: 15% chromatid gaps and

31% breaks. The highest number of breaks were associated with group B chromosomes. In similar experiments with HSV-1, the lack of legible metaphase plates in the control prevented any definite conclusions; it is suggested that the virus inhibited lymphocyte mitosis. With HSV-2, uninfected lymphocytes had 13.7% aberrations/cell: 5.3% breaks, 7.7% gaps, and 0.6% deletions. Infected cultures showed 28.8% aberrations/cell: 5.9% breaks, 22.2% gaps, and 0.7% deletions. The changes observed as gaps were mostly due to staining. It is concluded that vaccinia virus exerts a destructive effect on the chromosomal system of developing cells and that HSV-2 does not. The effect of HSV-2 probably results in transformation of the host cells. (19 refs.)

**78-0897 Production of Group- and Type-specific Antigens During Non-permissive Infection of Dog Kidney Cells with Herpes Simplex Virus Type 2.** (Eng) Patterson, W. R. (Dept. Microbiology, Univ. Texas Health Science Center at San Antonio, San Antonio, TX, 78284); Gauntt, C. J. *Biochem Biophys Res Commun* 80(1): 243-251; 1978.

The ability of African green monkey kidney (Vero) cells and Madin-Darby canine kidney (MDCK) cells infected with herpes simplex virus type 2 (HSV-2: 10-12 plaque-forming units/cell) to produce viral antigens and new virus was investigated. Infection of MDCK resulted in little or no new infectious virus, but Vero cells produced progeny virus. Serial subculture of MDCK cells inoculated with HSV-2 did not permit the establishment of carrier cell cultures. Group- and type-specific antigens were detected in lysates of nonpermissive MDCK cells inoculated with HSV-2 by 24 hr postinoculation. In the MDCK cells, two high-mol-wt polypeptides not found in uninfected MDCK cells were synthesized. One of these comigrated with a major HSV-2 structural polypeptide. HSV-2 may undergo abortive infection in human cervical cells, as it does in abortively infected MDCK cells, which would account for the HSV-2 antigens in the former. (17 refs)

**78-0898 Physical Mapping of Genes and Crossover Events by Analysis of Herpes Simplex Virus Intertypic Recombinants** (Meeting Abstract). (Eng) Brown, V. G. (Inst. Virology, Church St., Glasgow, G11 5JR, Scotland); Marsden, H. S.; Cortini, R.; Timbury, M. C.; Subak-Sharpe, J. H.; Wilkie, N. M. *Heredity (Lond)* 39(3): 434; 1977. (no refs)

**78-0899 Adenovirus DNA Synthesis In Vitro in an Isolated Complex.** (Eng) Frenkel, G. D. (Dept. Microbiology and Immunology, Neil Hellman Medical Res. Building, Albany Medical Coll., Albany, NY, 12208). *J Virol* 25(1): 459-463; 1978.



The role of DNA polymerase in adenovirus DNA synthesis was investigated in vitro, in adenovirus-infected KB cells. DNA-protein complexes were isolated from the virus-infected cells by a modification of the M-band technique. In vitro synthesis was semiconservative, inhibited by N-ethylmaleimide, and stimulated by ATP. Studies with adenovirus H5 ts36 and H5 ts125 (DNA- negative mutants) indicated that in vitro DNA synthesis represented a continuation of in vivo replication. In vitro synthesis was inhibited 38% by 20  $\mu$ g/ml phosphonoacetic acid; similar results were obtained with DNA polymerase  $\alpha$ ; less inhibition was obtained with the DNA polymerases  $\beta$  and  $\gamma$ . Synthesis in complexes from uninfected cells was much less sensitive to inhibition by phosphonoacetic acid. Furthermore, complexes from infected cells contained a greater proportion of  $\alpha$ -polymerase than complexes from uninfected cells, suggesting that an association of  $\alpha$ -polymerase with the replication complex may occur during adenovirus infection, with subsequent utilization of this enzyme for viral DNA synthesis. (20 refs.)

- 78-0900 Transcription of Adenovirus-associated Virus RNA in Isolated KB Cell Nuclei.** (Eng) Bloom, M. E. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014); Rose, J. A. *Virology* 84(1): 118-126; 1978.

The transcription of the genomes of adenovirus-associated virus (AAV) type 2, a defective parvovirus, and adenovirus (Ad) type 2, a helper virus, was studied in nuclei from infected KB cells. As measured by  $^3$ H-uridine triphosphate incorporation into acid-insoluble product, nuclei prepared 15.5 hr after coinfection with AAV and Ad (AAV-Ad nuclei) synthesized RNA for 10 min. Total RNA synthesis in AAV-Ad nuclei was greater than that in uninfected nuclei, but it was one-half that in nuclei from cells infected with Ad alone (Ad nuclei). DNA-RNA hybridization analysis revealed that the in vitro synthesis of AAV-RNA (14% of total) was twice that of Ad-RNA (6% of total). Total RNA synthesis in Ad and AAV-Ad nuclei was comparable until 12 hr postinfection, after which the synthesis declined in AAV-Ad nuclei. However, from 12 hr on, more AAV-RNA than Ad-RNA was synthesized in AAV-Ad nuclei; a comparison with Ad nuclei suggested a preferential inhibition of Ad-RNA transcription in the AAV-Ad nuclei. Ninety-five percent of the Ad-RNA synthesis and > 99% of the AAV-RNA synthesis were inhibited by  $\alpha$ -amanitin at levels that blocked cellular RNA polymerase II activity. The results suggest that the AAV genome is transcribed by the same polymerase that transcribes the bulk of Ad-RNA and cellular heterogeneous nuclear RNA. (30 refs)

- 78-0901 Effect of Protein Synthesis Inhibitors on Viral mRNA's Synthesized Early in Adenovirus Type 2 Infection.** (Eng) Eggerding, F. (Dept. Pathology, Div. Bi-

ology and Biomedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO, 63110); Raskas, H. J. *J Virol* 25(1): 453-458; 1978.

The effect of cycloheximide (CH) on viral messenger RNA's (mRNA's) synthesized early in adenovirus type 2 infection was investigated, and the results were compared with those from experiments performed in the absence of CH or in the presence of the DNA synthesis inhibitor 1- $\beta$ -D-arabinofuranosylcytosine (araC). Compared with mRNA species synthesized in the absence of CH or in the presence of 20  $\mu$ g/ml araC, CH (25  $\mu$ g/ml) stimulated the accumulation of  $^3$ H-uridine into early viral mRNA species tenfold. The only exception was a 24S mRNA transcribed from the trans-forming end of the genome; accumulation of this species was stimulated no more than twofold. CH also resulted in the accumulation of polyadenylated RNA's transcribed from *Eco*RI-C that were heterogeneous and smaller than the 20S mRNA. Treatment of cells with  $5 \times 10^{-7}$  M pactamycin,  $10^{-6}$  M puromycin, or  $10^{-6}$  M emetine produced similar effects. These findings suggest that the inhibition of protein synthesis early after infection alters the metabolism of specific RNA sequences. (35 refs.)

- 78-0902 A Rapid and Inexpensive Procedure for the Purification of Adenovirions.** Brief Report (Eng) Lentfer, D. (Virologische Abteilung, Instituts für Hygiene und Mikrobiologie, Universität des Saarlandes, D665 Homburg, W. Germany); Conde, C. *Arch Virol* 56(1/2): 189-193; 1978.

A procedure was developed for the purification of adenovirions that involves extraction with chloroform and two cycles of simultaneous sedimentation velocity and isopycnic centrifugation through a glycerol layer onto a performed KBr gradient. This procedure gave 99% pure adenovirions in 8 hr. The specific infectivity of the purified virus was  $1.8 \times 10^{11}$  TCID<sub>50</sub>/mg protein, and its buoyant density in KBr was 1.332 g/cm<sup>3</sup>. (4 refs)

- 78-0903 Studies of the Transcription of Viral Genome Adenovirus 5 Transformed Cells.** (Eng) Frolov, E. I. (Inst. Molecular Biology, Academy Sciences, Moscow, USSR); Zalmanzon, E. S.; Lukanidin, E. M.; Georgiev, P. *Nucleic Acids Res* 5(1): 1-12; 1978.

The transcription of adenovirus type 5 (Ad5) DNA was studied in transformed rat embryo cells (line DFK3) by two methods: (1) hybridization of in vivo-labeled  $^{32}$ P-RNA with restriction fragments of viral DNA and (2) reassociation of viral DNA fragments in the presence of transformed cell DNA that had been selectively digested with DNase I. The data showed that not all the Ad5 DNA sequences present



K3 cells are transcribed. There were 2.5 copies of the *HpaI*-E fragment of the Ad5 genome per diploid quantity of K3 cell DNA. Hybridization of the nuclear RNA from K3 cells to separated restriction fragments of Ad5 DNA showed that only the C, D, E, and F fragments are transcribed. Although some sequences of *HpaI* fragments A and B were present in the DFK3 cells (0.6 copy/diploid quantity of DNA), RNA transcripts complementary to these fragments could not be detected in the nuclei. Only 50% of the sequences of the *HpaI*-E fragment were sensitive to DNase digestion of DFK3 cell nuclei. Thus, not all the sequences of this fragment are active in transcription and/or only 50% of the length of the *HpaI*-E is transcribed and sensitive to the digestion. (21 refs)

78-0904 **Some Adenovirus DNA Is Associated with the DNA of Permissive Cells During Productive or Restricted Growth.** (Eng) Tyndall, C. (Dept. Microbiology, Curtin Sch. Medical Res., Australian Natl. Univ., Canberra, A.C.T., Australia); Younghusband, H. B.; Bellett, A. *J. Virol* 25(1): 1-10; 1978.

The association of viral DNA with cell DNA was investigated in chicken embryo kidney (CEK) cells productively infected with chicken embryo lethal orphan (CELO) virus and in human (HEK) cells infected with the temperature-sensitive mutants *ts36* and *ts125* of human adenovirus type 5 under permissive and restrictive conditions. Cell and free viral DNA molecules were separated at 36 hr after CELO virus infection of CEK cells by methods that rely on different DNA properties: alkaline sucrose gradient centrifugation, DNA reannealing kinetics, and cesium chloride density gradient centrifugation. The cell DNA was then tested for viral sequences. Between 500 and 1,000 viral DNA equivalents were associated with cell DNA purified by each method. This quantitative agreement suggests that CELO virus DNA is integrated into chick cell DNA during infection. In similar experiments with HEK cells and *ts125*, the same proportion of viral DNA was associated with cell DNA in the absence of viral DNA replication. This suggests that viral replication is not necessary for integration and that the difference (50-fold) in transformation frequency between these mutants is not due to a difference in their frequency of integration. (41 refs.)

78-0905 **Two Initiation Sites for Adenovirus 5.5S RNA.** (Eng) Vennstrom, B. (Dept. Microbiology, Biomedical Center, Uppsala Univ., Uppsala, Sweden); Pettersson, U.; Philipson, L. *Nucleic Acids Res* 5(1): 195-204; 1978.

The second 5'-terminal sequence of adenovirus-specific 5.5S RNA, which was initiated with adenosine tetraphosphate, was identified using adenovirus 2-infected HeLa cells. Complementary pancreatic RNase digests of the RNA showed that it

contained the 5'-terminal oligonucleotide sequence (pp)pApGpCp in addition to the major 5'-terminal sequence (pp)pGpGpGpCp. Thus, 5.5S RNA can initiate with guanosine and adenosine tetraphosphate. Around 25% of the 5.5S RNA initiates with (pp)pAp, 75% with (pp)pGp. Since the sequence AGC does not occur until position 153, and since both 5.5S RNA species are similar in length and have nearly identical RNase T1 fingerprints, it is concluded that the start of the (pp)pAp species is located three nucleotides to the left of the site where the guanosine-initiated RNA starts. The two termini were detected early (2-6 hr) and late (14-18 hr) after infection. In isolated nuclei, 200 µg/ml α-amanitin inhibited all 5.5S RNA transcription, indicating that both initiation sites are recognized by RNA polymerase III. (19 refs)

78-0906 **Physicochemical Properties of Human Adenovirus Type 6.** (Rus) Dubichev, A. G. (D. I. Ivanovsky Inst. Virology, Moscow, USSR); Parfenov, N. N.; Chaplygina, N. M.; Borovik, A. S.; Dreizin, R. S.; Zolotarevskaya, E. E.; Tikhonenko, T. I. *Vopr Virusol* (1): 47-51; 1978.

Various physicochemical characteristics of human adenovirus type 6 DNA were studied. The mol wt of the DNA molecule, based on the sedimentation constant (32.7S) and the characteristic viscosity (93.8 daltons/g), was  $23.2-23.5 \times 10^6$  daltons. The av amount of guanosine-cytidine pairs determined in a heat denaturation assay was 51.75%. (23 refs)

78-0907 **Integrated Viral Sequences in Adenovirus Type 12-transformed Hamster Cells.** (Eng) Groneberg, J. (Inst. Genetics, Univ. Cologne, Cologne, W. Germany); Chardonnet, Y.; Doerfler, W. *Cell* 10(1): 101-111; 1977.

The physical state of the viral genome was investigated in four lines of hamster cells transformed by adenovirus type 12 (Ad12) following infection at multiplicities ranging from 5 to 350 plaque-forming units per cell. The DNA from transformed cells was restricted at 51.7 and 94.6 fractional length units with the Sal I endonuclease from *Streptomyces albus*. This enzyme was found to cleave hamster cell DNA from transformed cells less frequently than adenovirus DNA per unit length of DNA. After cleavage by the Sal I enzyme, it was possible to separate free adenovirus DNA sequences from those covalently linked to cellular DNA in transformed hamster cells. Sequential hybridization experiments were performed in which the Sal I fragments of the DNA from Ad12-transformed hamster cells were first hybridized to Ad12 DNA on filters, eluted from the filters, and then hybridized to hamster cell DNA. They indicate that the Sal I fragments of the transformed cells contain covalently linked viral and cellular sequences. The cellular DNA sequences attached to viral DNA were further characterized by reassociation ki-



netics, which confirmed the data obtained in the filter hybridization experiments. It is concluded that the Ad12 DNA in transformed hamster cells persists at least in part in the integrated state. (27 refs.)

- 78-0908 T Antigen Synthesis and Resistance to Interferon in Human Adenovirus Type 12 Infected Chick Cells.** (Eng) Pusztai, R. (Inst. Microbiology, Univ. Medical Sch., 6720 Szeged, Hungary); Szabo, E.; Beladi, I. *Acta Virol (Praha)* 21(6): 449-455; 1977.

Type-specific T-antigen and interferon formation were demonstrated in adenovirus type 12 infected chick embryo cells. Cycloheximide (5-10 µg/ml) inhibited T-antigen formation, but cytosine arabinoside (<40 µg/ml) and exogenous chick interferon had no effect. Virus-specific structural antigen could not be detected in these cells. (16 refs)

- 78-0909 Antibody Response to Adenovirus Type 12 T Antigen in Tumor-bearing Rats (Meeting Abstract).** (Eng) Morrongiello, M. P. (Rutgers Medical Sch., Piscataway, NJ, 08854); Raska, K. *Fed Proc* 37(3): 412; 1978. (no refs)

- 78-0910 International Workshop on Hepatitis B and Liver Cancer: Special Report.** (Eng) Ziegler, J. L. (Clinical Oncology Program, Div. Cancer Treatment, NCI, NIH, U.S. Dept. Health, Education, and Welfare, Bethesda, MD, 20014); Adamson, R. H.; Barker, L. F.; Fraumeni, J. F.; Gerin, J.; Purcell, R. H. *J Natl Cancer Inst* 60(3): 717; 1978.

According to data presented at an international workshop on liver cancer, hepatitis B virus (HBV) infection leads to chronic liver damage, and further exposure to hepatocarcinogens such as aflatoxin B<sub>1</sub> can initiate cancer. Widespread HBV vaccination should be used in endemic areas to reduce the incidence of primary hepatocellular carcinoma. (no refs)

- 78-0911 Hepatitis B and Cancer of the Liver.** (Fre) Sankale, M. (Clinique Medicale de la Faculte de Medecine et de Pharmacie, Dakar, Senegal). *Bull Acad Natl Med* 161(6): 492-495; 1977.

Ninety-two percent of all Senegalese patients with malignant hepatoma were found to be carriers of active hepatitis B virus infection. Hepatitis B surface antigen tests were positive in 61.2% of the hepatoma patients, 71.4% of the patients with liver cirrhosis, and 84.6% of the patients with hepatitis vs 11.5% of healthy subjects.

The incidences of anti-HBs-positive tests were 18.2% in hepatoma, 17.1% in cirrhosis, and 2.5% in hepatitis vs 38% in healthy subjects. The incidences of anti-HBc positive tests were 87.3% in hepatoma, 88.6% in cirrhosis and 100% in hepatitis vs 25% in the control. The findings indicate that hepatitis B virus is probably an important factor in hepatoma induction but that does not have intrinsic oncogenic properties. It is not a constant and indispensable factor in the induction of hepatoma; it may act in association with other as yet unidentified or little-known factors. (4 refs)

- 78-0912 Hepatitis B Surface Antigen and  $\alpha$ -Fetoprotein in Patients with Hepatocellular Carcinoma (Letters to Editor).** (Eng) Chen, D. S. (Dept. Internal Medicine, Coll. Medicine, Natl. Taiwan Univ., Taipei, Taiwan, 100, Republic China); Sung, J. L.; Kubo, Y.; Okuda, K. *Gastroenterology* 74(1): 163-165; 1978.

A study of 93 Taiwanese patients with hepatocellular carcinoma indicated that serum  $\alpha$ -fetoprotein (AFP) is not related to the prevalence or titer of hepatitis B surface antigen (HBsAG) and that HBsAG may persist throughout the course of the disease. Other investigators also indicate that the previously observed positive association between AFP and HBsAG is not always valid. However, it is stated that there is a trend for HBsAG to increase during the course of the disease, often coincident with rapid tumor growth. (no refs.)

- 78-0913 Familial HBsAg-positive Hepatoma: Treatment with Orthotopic Liver Transplantation and Specific Immunoglobulin.** (Eng) Johnson, P. J. (Liver Unit, Kings Coll. Hosp. and Medical Sch., London SE5, England); Wansbrough-Jones, M. H.; Portman, B.; Eddleston, A.; Williams, R.; Maycock, W.; Calne, R. Y. *Br Med J* 1(610): 216; 1978.

Two of three brothers, both positive for hepatitis B surface antigen, developed hepatocellular carcinoma. The one brother that survived was treated by liver transplantation, and received large doses of specific immunoglobulin to prevent reinfection of the donor liver by HB virus. A common genetic susceptibility is suggested. (5 refs)

- 78-0914 The Relationship Between Hepatitis B Virus Infection and Hepatic Cell Carcinoma in Mozambique.** (Eng) Reys, L. L. (Dept. Pharmacology, Faculty of Medicine, Univ. Eduardo Mondlane, Mozambique); Purcell, R. H.; Holland, P. V.; Alter, H. J. *Trop Geogr Med* 25: 251-256; 1977.

Sera from 32 African patients with hepatocellular carcinoma



and 275 healthy blood donors, including Europeans and members of four African subgroups, were tested for hepatitis surface antigen (HBsAg) and HB antibodies. The frequency of HBsAg was significantly higher (60%) among the cancer patients than among the blood donors (7%-15%). However, tests for antibody to HBsAg revealed no significant differences in exposure to HB virus between the cancer patients (44%) and the African blood donors (46%-52%). Exposure was significantly less frequent among the European blood donors (21%) compared with the African donors. It is concluded that HB virus does not play a primary role in the pathogenesis of hepatocellular carcinoma, although it may promote carcinogenesis through the development of chronic hepatitis with cirrhosis. (199 refs.)

78-0915 **Interrelation Between Cirrhosis and Cancer of the Liver.** (Rus) Khazanov, A. I. (No affiliation given). *Klin Med (Mosk)* 55(11): 76-81; 1977.

Of 528 patients with liver cirrhosis, 68 had primary cancer of the liver. Most often the cancer developed against a background of active cirrhosis. During the last decade, there has been an increase in malignancies in diseases of alcoholic and drug genesis and also in liver cirrhosis associated with circulatory insufficiency. The blood sera of some patients with cirrhosis and terminal cancer contained hepatitis B surface antigen, which pointed to super- and reinfection by serum hepatitis. Liver cirrhosis was observed in 1.3% and primary cancer in 0.11% of the patients with sustained virus hepatitis. (1 refs.)

78-0916 **Viruses Detected in a Transplantable Culture of Human Malignant Paraganglioma.** (Rus) Chevlyagin, V. Ya. (N. F. Gamaleya Inst. Epidemiology and Microbiology, Moscow, USSR); Klenova, A. V.; Chizovskaya, V. I.; Borodina, N. P.; Eremina, L. A. *Dokl Akad Nauk SSR* 237(2): 459-460; 1977.

An attempt was made to evaluate the possible activation of viral agent synthesis in transformed cell culture 63, which was derived from the primary culture of a human malignant paraganglioma. Centrifugation of labeled 63 in a sucrose density gradient showed the presence of two peaks, one corresponding to DNA-containing structures, one to RNA-containing structures. The biosynthesis of RNA viruses decreased after exposure of the cells to actinomycin D (0.5 µg/ml), but it was significantly elevated after treatment with mitomycin C. Inoculation of Vero cells and cells of embryonal tissue (RET), murine embryonal tissue (MET), chick embryonal tissue (CET), and hamster embryonal tissue (HET) with RNA virus did not result in cytodestruction or transformation. Mitomycin inhibited the biosynthesis of DNA-containing structures 24 hr after exposure but stimulated their

synthesis 120 hr later. Inoculation of Vero cells and RET cells with DNA-virus caused cytodestruction. Exposure to DNA-virus alone did not transform HET and RET cells, but exposure to both RNA- and DNA-containing structures transformed CET, Vero, HET, and RET cultures. (4 refs.)

78-0917 **A New Lymphoid Cell Line, Reh 6, with Characteristics of Non-T and Non-B Cells, Lacking the Epstein-Barr Virus Genome and Derived from Human Acute Lymphoblastic Leukemia.** (Eng) Kayibanda, B. (Institut de Cancerologie et d'Immunogenetique, Hopital Paul Brousse, 14, avenue Paul-Vaillant-Couturier, F-94800 Villejuif, France); Rosenfeld, C.; Goutner, A.; Bornkamm, G. W. *Intervirology* 9(5): 316-320; 1978.

A new lymphoid cell line, Reh 6, was established from the peripheral blood of a patient with acute lymphocytic leukemia (ALL), and it is being used for the active immunotherapy of ALL patients. Reh 6 cells, which lack T- and B-cell properties, were assayed for the presence of Epstein-Barr virus (EBV) DNA by nucleic acid hybridization and for Epstein-Barr nuclear antigen (EBNA) by the immunofluorescence test. In vitro reassociation kinetics between <sup>3</sup>H-EBV DNA and Reh 6 cell DNA indicated the absence of detectable amounts of EBV DNA in Reh 6 cell DNA. EBNA could not be detected in Reh 6 cells by the immunofluorescence test. The findings suggest that the Reh 6 cell line lacks the EBV genome. (17 refs.)

78-0918 **Immunological Demonstration of Oncornavirus Genome in Leucocytes of Myeloid Leukaemic and Preleukaemic Patients (Meeting Abstract).** (Eng) Toth, F. D. (Inst. Microbiology and Second Dept. Medicine, Univ. Medical Sch., Debrecen, Hungary); Jako, J.; Vaczi, L.; Rak, K.; Redai, I. *Acta Microbiol Acad Sci Hung* 24(1): 74; 1977. (no refs.)

78-0919 **A New Structure of Wart Virus Crystals (Meeting Abstract).** (Eng) Schremmer, C. N. (Zentralinstitut für Krebsforschung, Akademie der Wissenschaften der DDR, Berlin-Buch, z. Zt. Hamburg, W. Germany). *J Cutan Pathol* 4(4): 226-227; 1977. (no refs.)

78-0920 **Investigation of Human Urogenital Tract Tumors for Papovavirus Etiology: Brief Communication.** (Eng) Shah, K. V. (Dept. Pathobiology, Johns Hopkins Univ., Sch. Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD, 21205); Daniel, R. W.; Stone, K. R.; Elliott, A. Y. *J Natl Cancer Inst* 60(3): 579-582; 1978.

Cultured human urogenital cancers, other cancers, and normal tissues were examined by immunofluorescent antibody staining for the T and capsid antigens of BK virus (BKV), JC virus, and simian virus 40 (SV40) and for the capsid antigens of herpes simplex virus types 1 and 2 and human cytomegalovirus (CMV). Cells from early passage cultures of 123 primary tissues and 14 continuous lines from transition-



al or renal cell carcinoma were tested. None of the cell preparations stained specifically with any of the antisera. In a serologic study, the prevalence and titers of BKV hemagglutination-inhibiting and SV40-neutralizing antibodies were similar in bladder cancer patients, prostate cancer patients, and normal controls. None of the three groups had SV40 or BKV T antibodies. Among supernatants of primary cultures from 35 tissues, the only virus isolated was CMV. These results suggest that papovaviruses of the SV40-polyoma subgroup are not related etiologically to bladder and prostate cancer. (29 refs.)

- 78-0921 Electron Microscope Study of the Base Sequence Homology Between Simian Virus 40 and Human Papovavirus BK.** (Eng) Newell, N. (Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205); Lai, C. J.; Khoury, G.; Kelly, T. J. *J Virol* 25(1): 193-201; 1978.

The base sequence homology between the genomes of human papovavirus BK (BKV) and simian virus 40 (SV40) was studied by the electron microscope heteroduplex method. DNA molecules of the two viruses were cleaved once with endonuclease *R. EcoRI*, and heteroduplexes were constructed and mounted for microscopy in various concentrations of formamide to achieve various effective temperatures. At the lowest effective temperature tested (30% formamide;  $T_m$ -35°C), the BKV/SV40 heteroduplexes were 92% double-stranded and they contained only two single-stranded regions, whose locations mapped near the junctions between the early and late regions of the SV40 genome. At higher effective temperatures, the fraction of duplex DNA in the BKV/SV40 heteroduplexes decreased, indicating significant base mismatching in the homologous regions. The strongest regions of homology were located in the late region. (39 refs.)

- 78-0922 Immunological Relatedness of Papovaviruses of the Simian Virus 40-Polyoma Subgroup.** (Eng.) Shah, K. V. (Dept. Pathobiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD 21205); Daniel, R. W.; Kelly, T. J. *Infect Immun* 18(2): 558-560; 1977.

Viral antigen in rhesus monkey kidney cells infected with human JC virus or baboon SA12 virus and in mouse lung cells infected with murine K virus were reactive in immunofluorescence tests to antisera against sodium dodecyl sulfate-disrupted simian virus 40 (SV40) capsids and polyoma VP1. The major capsid polypeptides of all papovaviruses of the simian virus 40-polyoma subgroup are therefore immunologically related. (6 refs.)

- 78-0923 Ultrastructural Studies of H-1 Parvovirus Replication: VI. Simultaneous Autoradiographic**

**and Immunochemical Intranuclear Localization of Viral DNA Synthesis and Protein Accumulation.** (Eng) Singer, I. (Inst. Medical Res., Putnam Memorial Hosp., Bennington, VT 05201); Rhode, S. L. *J Virol* 25(1): 349-360; 1978.

The localization of the parvovirus H-1 viral replicative-form (RF) double-stranded DNA (dsDNA) and progeny single-stranded DNA (ssDNA) in parasynchronously infected simian virus 40 (SV40)-transformed newborn human kidney cells was studied by high-resolution electron microscope autoradiography. The proportion of the total DNA synthesis that was viral was > 90%, as estimated by comparing the amount of  $^3\text{H}$ -thymidine uptake in cultures infected with wild-type H-1 vs temperature-sensitive (*ts*) strain 14 (an H-1 mutant defective in DNA replication). Simultaneous staining with cytochrome c-conjugated anti-H-1 IgG confirmed that the cells incorporating  $^3\text{H}$ -thymidine were H-1-infected. The sites of H-1 RF (in *ts*1-infected cells; a conditional H-1 mutant defective in progeny ssDNA synthesis) and progeny wild-type-infected cells) DNA synthesis were identical. Both H-1 RF dsDNA and progeny ssDNA synthesis began at a small number of sites associated with extruded masses of nucleolar fibrous components localized in the euchromatin. In later stages of infection, following complete margination of the heterochromatin, viral DNA replication occurred in the euchromatin throughout the nucleus. The results suggest that H-1 proteins and cellular cofactors associated with the fibrous component of the nucleolus and the euchromatin may play a role in regulating H-1 DNA synthesis. (37 refs.)

- 78-0924 Replication Process of the Parvovirus H-1: Isolation of a Mutant Defective in Replicative-Form DNA Replication.** (Eng) Rhode, S. L. (Putnam Memorial Hosp. Inst. Medical Res., Bennington, VT 05201); *J Virol* 25(1): 215-223; 1978.

A temperature-sensitive mutant of parvovirus H-1, *ts*14, which is partially defective in replicative-form (RF) DNA synthesis, was isolated and characterized. At the restrictive temperature (39.5°C), *ts*14 plaque-forming ability and infectious virus production decreased. RF DNA synthesis of *ts*14 was reduced to 3%-7% of that of wild-type H-1 at either restrictive or permissive temperature. Complementation analysis of the RF DNA synthesis of *ts*14, a viable defective H-1 virus, DI-1 (with normal RF DNA replication level) and wild-type H-3 virus indicated that the defective RF DNA synthesis of *ts*14 is cis-acting. *ts*14, unlike wild-type H-1 virus, caused a multiplicity-dependent inhibition of DI-1 and H-3 but not LuIII, RF DNA synthesis. A multiplicity-dependent cross-interference for viral protein synthesis was also defined for H-1, H-3, or LuIII. *ts*14 inhibited the infectious virus production of H-1 or H-3, but not LuIII. LuIII- or pseudotype particles were produced by coinfection with H-3 DNA was more homologous than LuIII DNA to *ts*14 DNA by comparative physical-mapping studies. These studies suggest that *ts*14 has a mutation in a regulatory region of its DNA that influences RF DNA replication and the



proteins are not defective for RF DNA replication. (17 refs.)

**78-0925 The Isolation of Defective Variants of Simian Virus 40 Whose Genomes Contain Sequences Derived from Adenovirus 2 DNA.** (Eng) Sambrook, J. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11724). *J Gen Virol* 38(2): 313-327; 1978.

Hybrids between adenovirus 2 (Ad2+DI) DNA and simian virus 40 (SV40 *tsa* 30) DNA were isolated. Ad2+DI DNA was cleaved with various restriction endonucleases, mixed with SV40 *tsa* 30 DNA, and used to infect monolayers of CV1 cells. The hybrids isolated had closed circular genomes 5 to 10 kilobases in size. The structure of the genomes was complex, but in the simplest case, analysis by restriction endonuclease digestion and hybridization indicated that the adenovirus 2 DNA was present as a continuous block, of max size 10 kilobases. Different hybrids containing different segments of the adenovirus 2 genome were obtained. (35 refs.)

**78-0926 Comparison of Two Viable Variants of Simian Virus 40.** (Eng) Kay, A. C. (Lab. Biochemistry, NIH, Bethesda, MD 20014); Rao, G. R.; Singer, M. F. *J Virol* 25(1): 339-348; 1978.

The DNA's of two viable strains of simian virus 40 (SV40), 776 (small-plaque) and 777 (large-plaque), were compared using the use of restriction endonucleases in an attempt to relate differences between variant DNA's with alterations in viral-coded proteins. Differences between the two strains were detected at five points on the SV40 genome. One difference was a deletion of 0.5% of the strain 777 SV40 genome in the DNA region coding for the major viral coat protein, VP1. This difference was confirmed by tryptic peptide analysis of the coat proteins; it indicated that the 777 VP1 is missing one peptide found in the 776 VP1 but has at least two additional lysine peptides. Other differences are located in the DNA regions (1) at or near the termination point for replication and for early and late transcription, (2) within the early region of transcription, and (3) near the origin of DNA replication. DNA synthesis rates were similar with both 776 and 777, but 776 consistently yielded only 1/10 to 1/4 the number of plaque-forming units as 777. Defective variants derived from strain 777 interfered more efficiently with strain 776 replication than with 776 replication. The physiological differences and specificity of interference of the defective variants may be related to the alterations in VP1. (41 refs.)

**78-0927 Effect of Input Multiplicity on the Establishment of Simian Virus 40 Persistent Infections in Rhesus Monkey Kidney Cells.** (Eng) Norkin, L. C. (Dept. Microbiology, Univ. Massachusetts, Amherst, MA 01003). *Infect Immun* 18(3): 868-871; 1977.

Experiments were conducted to determine whether simian virus 40 (SV40)-rhesus monkey kidney cell carrier systems can also be established after infection at low multiplicities of infection (MOI). Subconfluent monolayer cultures of LLC-MK<sub>2</sub> rhesus monkey kidney cells were infected with SV40 at MOI of 100, 10, and 1 plaque-forming units/cell. Cultures were then sampled to measure the fraction of SV40 T- and V-antigen-producing cells, nonviable trypan blue-stainable cells, and viral yields. Initially, approx 40% of the cells were infected at the highest MOI, 2% at the lowest. However, the fraction of infected cells in the high-input cultures decreased to 16% within 22 days, but that in the low-input cultures increased to 100%. Eight weeks were required before the high-input cultures were completely infected. The fraction of V-antigen-producing cells became substantially lower than the fraction of T-antigen-producing cells, indicating that productive infection was perpetuated by only a fraction of those cells that carry the SV40 genome. Defective interfering particles and interferon production were not seen during the first 10 wk. Their appearance at later times probably serves to regulate and stabilize the infection further. It is suggested that host cell factors are of primary importance during the early stages of infection. (12 refs.)

**78-0928 Alteration of Cell Surfaces With Increased Tumorigenicity.** (Eng) Steplewski, Z. (ul. Czerska 12, 43-114 Wroclaw, Poland); Kilarski, W.; Grabska, A. *Arch Immunol Ther Exp (Warsz)* 25(3): 331-339; 1977.

Four lines of simian virus 40-transformed male BALB/c mouse peritoneal macrophages (MMSV) were studied for tumorigenicity of inocula, saturation density, agglutinability by concanavalin A (Con A), and surface morphology as revealed by scanning electron microscopy. The MMSV cells were cultured in vitro and then injected into syngeneic mice; cells from the resulting tumor were designated GMMSV<sub>1</sub>. This procedure was repeated twice, resulting in GMMSV<sub>1</sub> and GMMSV<sub>2</sub> cells. The four lines showed no limits in saturation density and no growth inhibition; however, GMMSV<sub>1</sub>, GMMSV<sub>2</sub>, and GMMSV<sub>3</sub> had significant decreases in saturation density when they were maintained at confluence, with no medium changes. Lowest Con A agglutinability was observed in MMSV; GMMSV<sub>1</sub> showed higher agglutinability, but the other two lines had twice as much agglutinability as MMSV cells. Tumorigenicity was studied by sc or ip injections in BALB/c mice. The cells that had undergone repeated passage in syngeneic hosts had higher levels of tumorigenicity. The ultrastructural changes appeared to be related directly to an increasing tendency to form tumors. (28 refs.)

**78-0929 Parallel Induction of Sister Chromatid Exchanges and Infectious Virus from SV40-transformed Cells by Alkylating Agents.** (Eng) Kaplan, J. C. (Infectious Disease Unit, Massachusetts General Hosp., Boston, MA 02114).



ton, MA, 02114); Zamansky, G. B.; Black, P. H.; Latt, S. A. *Nature* 271(5646): 662-663; 1978.

The relationship between virus induction and sister chromatid exchanges (SCE) was investigated in simian virus 40-transformed hamster kidney cells of clones A, E, and B and the nonproducing, noninducible clone G. Treatment of clone G with 0.03  $\mu\text{g}/\text{ml}$  mitomycin C increased the av frequency of SCE from 11/metaphase to 88/metaphase. When cells from the other lines were treated with 0-0.05  $\mu\text{g}/\text{ml}$  mitomycin C or 0-500  $\mu\text{g}/\text{ml}$  ethyl methane sulfonate, the av frequency of SCE increased in proportion to the dose of the inducing agent. Chromosomal aberrations increased with increasing dose, but they were not always detected at the lowest doses, as were SCEs. Virus yields paralleled SCE frequency in their response to both alkylating agents. Absolute levels of virus production in the three clones were different, but the relative response remained the same. Cell survival was approx the same for each virus-producing line within the concentration ranges of either agent used. The exact relation between SCE formation and virus induction is unknown. (23 refs)

**78-0930 Oncogenic Transformation of 3T3 Cells Is Associated With Conversion from an 'Adult' to an 'Embryonic' Esterase Isoenzyme Pattern.** (Eng) Shier, W. T. (Cell Biology Lab., Salk Inst., San Diego, CA, 92112); Trotter, J. T. *Exp Cell Res* 111(2): 285-294; 1978.

Esterase isoenzyme patterns were examined in the cloned mouse fibroblast cell line 3T3 and two sublines transformed by simian virus 40 (SV3T3) and polyoma virus (Py3T3). Soluble enzyme preparations were prepared from SV3T3, Py3T3, mouse embryo (ME), and growing and nongrowing touching 3T3 cells and analyzed by discontinuous polyacrylamide slab gel electrophoresis. The esterases from SV3T3 and Py3T3 cells exhibited an isoenzyme pattern similar to that of primary ME cells but distinct from that of 3T3 cells. The pattern exhibited by 3T3 cells was similar to that of primary and secondary fibroblastoid cells derived from adult Swiss mouse kidney, suggesting that 3T3 is an adult cell line despite its origin as ME cells. The enzyme pattern was similar in growing and nongrowing 3T3 cells, although the specific activity was higher in preparations from nongrowing cells. The esterase and amidase activities were substantially higher in three subcellular fractions from virus-transformed 3T3 fibroblasts than in the corresponding fractions from 3T3 mouse fibroblasts or from primary ME cells. The largest increases in activity associated with viral transformation were observed in membrane-associated esterases. (31 refs.)

**78-0931 Altered Growth Behavior of Virus-transformed Cells after Treatment with Dextran Sulfate.** (Eng) Goto, M. (Dept. Oncology, Res. Inst. Tuberculosis,

Leprosy and Cancer, Tohoku Univ., Hirose-machi 4-12, Sendai 980, Japan); Hosaka, S.; Sasaki, S.; Sato, H. *Gann* 68(1): 73-80; 1977.

The in vitro growth behavior of 3T3 cells and 3T3 cells transformed by simian virus 40 (SV40) or polyoma (Py) was studied after treatment with dextran sulfate (0 to 20  $\mu\text{g}/\text{ml}$ ). The initial growth response of the SV3T3 and Py3T3 cells was similar to that of the untreated cells. When the transformed treated cells began to contact each other, however, the growth rate decreased and the cells reached a low density. With SV3T3 cells, the ratio of the saturation density of the untreated cells to that of the treated cells was 64.1% at 5  $\mu\text{g}/\text{ml}$  dextran sulfate and 43.4% at 10  $\mu\text{g}/\text{ml}$ . With Py3T3 cells, the ratio was 45.0% at both 10 and 20  $\mu\text{g}/\text{ml}$ . The growth rate of the 3T3 cells was suppressed slightly, but the cells reached almost the same saturation density as the untreated cells. The plating efficiency of 3T3 cells was not affected by treatment, but the treated transformed cells had a slightly higher plating efficiency than untreated cells. Treated cells showed a tendency to form thin, spread-out colonies in the central area. The treated SV3T3 and Py3T3 cells were flatter than the untreated cells. In agar, the treated transformed cells tended to stop growing after the formation of small colonies, but untreated cells continued to form large colonies. It is suggested that dextran sulfate temporarily altered the growth of the transformed cells to that of untransformed cells. (24 refs.)

**78-0932 Transcription of Host Substituted Simian Virus 40 DNA in Whole Cells and Extracts.** (Eng) Kuff, E. L. (Laboratory of Biochemistry, National Cancer Institute, Bethesda, MD, 20014); Ferdinand, F. J.; Khoury G. *J Virol* 25(1): 28-36; 1978.

The RNA synthesized in African green monkey kidney cells infected with wild-type simian virus 40 (SV40) and in BSC-1 cells containing a high proportion of host-substituted DNA molecules was examined. The relative labeling of the two types of host sequences was commensurate with their proportion in the viral DNA (about 20% host). The substituted virus contained both reiterated and unique cellular sequences and both types appeared to be transcribed. Transcripts of the substituted sequences formed a much smaller proportion of the virus-related RNA recovered from intact infected cells, suggesting that host sequence transcripts are synthesized but rapidly degraded in the whole cell. However, the possibility that transcription of these sequences is artificially enhanced in vitro cannot be excluded. The self-annealing of viral RNA's from nuclear extracts of cells infected with wild type and substituted viruses were compared. Transcripts labeled both in vivo and in vitro had two to three times the level of self-annealing with the variant than with wild-type SV40. These findings indicate that transcriptional complexes from substituted SV40 virus can be used to study localization of viral and cellular promoters, the basis for strand selection



al transcription and post-transcriptional processing of vi-  
and host RNAs. (34 refs.)

0933 **Binding and Transcription of Simian Virus 40  
DNA by DNA-dependent RNA Polymerase**  
*in Escherichia coli*. (Eng) Hale, P. (Dept. Microbiology,  
iv. Alabama in Birmingham, Birmingham, AL 35294);  
bowitz, J. *J Virol* 25(1): 298-304; 1978.

number, relative spectral changes, and locations of *Es-*  
*cherichia coli* RNA polymerase binding sites on supercoiled  
and nonsupercoiled simian virus 40 (SV40) DNA were deter-  
mined using difference spectroscopy, rifampin inhibition, and  
acrylamide gel electrophoresis. Supercoiled SV40 DNA  
was transcribed 2.5 times more efficiently by RNA polymere-  
se from *E. coli* than was nicked circular DNA. The effect  
was increased to fivefold when 4  $\mu$ g/ml rifampin was added  
with the triphosphates. Nine polymerase binding sites were  
determined by UV difference spectroscopy. These binding  
sites were located in the *Hin* II-III endonuclease fragments  
B, D, E, F, and G, as determined by gel electrophoresis.  
The number of sites was the same for both supercoiled and  
nicked or *Hin* II-III-digested DNA. The point of saturation  
for supercoiled DNA by polymerase remained the same with  
4  $\mu$ g/ml rifampin, which suggests that all binding sites on  
supercoiled DNA molecule have similar binding tight-  
nesses at 37 C and that the number of binding sites remains  
the same with or without rifampin. It is suggested that the  
difference in template ability between supercoiled and non-  
supercoiled DNA may be due to a difference in polymerase  
binding strength. (22 refs.)

0934 **Effect of Chemical Modification of Supercoiled  
Simian Virus 40 DNA on the Rate of In Vitro  
Transcription**. (Eng) Hale, P. (Dept. Microbiology, Univ. Ala-  
bama in Birmingham, Birmingham, AL 35294); Lebowitz,  
J. *J Virol* 25(1): 305-311; 1978.

Effect of the single-strand-specific reagent N-cyclohexyl-  
 $\beta$ -(4-methylmorpholinium)ethylcarbodiimide (CMC) on  
the template ability of supercoiled simian virus 40 (SV40)  
DNA was studied. A limited reaction of 2% of the DNA base  
pairs resulted in almost total inhibition of in vitro transcrip-  
tion by the DNA-dependent RNA polymerase from *Es-*  
*cherichia coli*. This effect was due to DNA modification and  
not to inhibition of polymerase activity. Studies of template  
saturation with polymerase showed that the inhibition of  
transcription by DNA modification is due to a loss of binding  
ability of the enzyme to the reacted, supercoiled DNA when  
reaction times of < 2 hr were used. It is concluded that a  
very limited modification of supercoiled SV40 DNA is re-  
sponsible for the loss of template function following CMC  
reaction and that polymerase binding is the major transcrip-  
tion step inhibited by CMC modification. (22 refs.)

78-0935 **Capping Structures of Simian Virus 40 19S and  
16S mRNAs**. (Eng) Groner, Y. (Dept. Virology,  
Weizmann Inst. Science, Rehovot, Israel); Carmi, P.; Aloni,  
Y. *Nucleic Acids Res* 4(11): 3959-3968; 1977.

The 19S and 16S messenger RNA's (mRNA's) from simian  
virus 40 (SV40)-infected BSC-1 cells were isolated and  
analyzed. The 19S mRNA had equal amounts of 5'  
caps  $m^7GpppAm$  and  $m^7Gpppm^6Am$ , but the 16S  
RNA contained mostly  $m^7Gpppm^6Am$ . This indi-  
cates that the 19S mRNA could be contaminated with  
some of the 16S species.  $N^6$ -Methyladenosine was  
found within the RNA chains of both species. (27 refs.)

78-0936 **Nucleotide Sequence of the Genes for the Simi-  
an Virus 40 Proteins VP2 and VP3**. (Eng) Red-  
dy, V. B. (Dept. Human Genetics, Yale Univ. Sch. Medicine,  
New Haven, CT, 06510); Dhar, R.; Weissman, S. M. *J Biol  
Chem* 253(2): 621-630; 1978.

The nucleotide sequence of simian virus 40 DNA comple-  
mentary to the 5' end of the messenger RNA (mRNA) for  
the viral structural proteins VP2 and VP3 was determined.  
The results indicate that the mRNA for the two proteins is  
read in the same phase and that the initiation site for VP3  
is within the structural gene of VP2. The codons of the  
COOH-terminal amino acids of VP2 and VP3 are read in a  
second phase as the codons of the NH<sub>2</sub>-terminal amino acids  
of VP1. (22 refs)

78-0937 **The Binding Site on SV40 DNA for a T Antigen-  
related Protein**. (Eng) Tjian, R. (Cold Spring  
Harbor Lab., Cold Spring Harbor, NY, 11524). *Cell* 13(1):  
165-179; 1978.

A protein closely related to simian virus 40 (SV40) tumor (T)  
antigen was purified in biologically active form from HeLa  
cells infected with the defective adenovirus-SV40 hybrid,  
Ad2 + D2, and its DNA binding sites were investigated. This  
107,000-dalton hybrid protein bound to a specific portion of  
SV40 DNA and protected it from digestion by pancreatic  
DNase I. Hybridization, endonuclease cleavage, and pyrimi-  
dine trace analysis of the protected fragments revealed that  
the D2 hybrid protein binds in a sequential manner to tandem  
recognition sites that lie within a sequence of 120 nucleotides  
at position 67 near the origin of SV40 replication. This find-  
ing lends support to the hypothesis that T-antigenlike pro-  
teins have a direct role in initiating SV40 DNA replication.  
Throughout the region of the binding sites, there are short  
repetitive sequences (GCC TCC) that may be recognized  
specifically by the D2 hybrid protein. However, the true  
recognition sequence within the binding sites has not been  
determined. (50 refs)



**78-0938 T Antigen and Initiation of Cell DNA Synthesis in a Temperature-sensitive Mouse Line Transformed by an SV40ts A Mutant and in Heterokaryons of the Transformed Cells and Chick Erythrocytes.** (Eng) Dubbs, D. R. (Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX, 77030); Trkula, D.; Kit, S. *Biochem J* 4(1): 95-110; 1978.

The role of simian virus 40 (SV40) gene A product in the initiation of cellular DNA synthesis was investigated using a mouse kidney line (mKSA207) transformed by the temperature-sensitive SV40 mutant SV40tsA207. mKSA207 cells were temperature-sensitive for growth, lost SV40 tumor (T) antigen (Tag) when incubated in low serum (0.5%) at 40 C, and accumulated Tag in the cytoplasm when fed 10% serum and incubated at the nonpermissive temperature (39.7 C). Following serum addition, the percentage of mKSA207 cells synthesizing DNA was the same at nonpermissive and permissive temperatures (33.5 C), suggesting that mKSA207 cells can traverse the cell cycle and initiate a new round of DNA synthesis at the nonpermissive temperature. The cells entered the S phase asynchronously at both temperatures, but most cells entered S within 16 hr and before Tag accumulated. mKSA207 cells synchronized by a double thymidine block also synthesized DNA at 39.7 C and entered a second S phase. Tag-depleted or Tag-synchronized mKSA207 cells, when fused with chick erythrocytes (CE), activated CE DNA synthesis. At 39.7 C, 40% of CE nuclei in heterokaryons with Tag-depleted mKSA207 cells displayed <sup>3</sup>H-thymidine-labeled nuclei 28-40 hr after fusion, when only 12% of CE nuclei were Tag+. These results indicate that SV40 gene A product probably does not have a direct role as an initiator of cellular DNA synthesis. (31 refs)

**78-0939 Isolation and Characterization of T Antigen-negative Revertants from a Line of Transformed**

**Rat Cells Containing One Copy of the SV40 Genome.** (Eng) Steinberg, B. (SUNY at Stonybrook, Stonybrook, NY 11594); Pollack, R.; Topp, W.; Botchan, M. *Cell* 13(1): 19-31; 1978.

Density-sensitive revertants were isolated by 5-fluoro-2-deoxyuridine (FUDR) selection from an established rat embryo line fully transformed by simian virus 40 (SV40) DNA. This line, 14B, contains nuclear tumor (T) antigen, grows to a high density, grows in low serum, and is anchorage independent. The revertants are all T-antigen-negative, density-sensitive, more serum-sensitive than 14B, and anchorage dependent. One group of revertants contains genome length SV40 DNA, one group contains SV40 DNA that has undergone a deletion, and the third group contains no detectable SV40 DNA. This heterogeneity is not a result of long-term passage, because the revertants arose with a frequency of  $10^{-5}$  in  $8.4 \times 10^5$  cells after as few as 12 passages. These findings suggest that there is a direct role for the functioning viral genome in the maintenance of the transformed state and that in the case of 14B, the phenotypes of transformation are not virus gene dosage-dependent. (49 refs)

See also:

\*(Rev.): 78-0641, 78-0642, 78-0643, 78-0644, 78-0645, 78-0646, 78-0647, 78-0648, 78-0649, 78-0650, 78-0661, 78-0664.

\*(Chem.): 78-0728, 78-0729, 78-0778.

\*(Immun.): 78-0943, 78-0949, 78-0957, 78-0960, 78-0970, 78-0971, 78-0972, 78-0973, 78-0977, 78-0982, 78-0985, 78-0988, 78-0990.

\*(Path.): 78-1035, 78-1059.

\*(Epid.-Biom.): 78-1105.



## IMMUNOLOGY

0940 **Immunologic Control of the Ascites Form of Murine Adenocarcinoma 755. I. Protection with Syngeneic Immune Serum or Lymphoid Cells.** (Eng) Haas, D. E. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC 27710); Roloson, G.; Collins, J. J.; Wells, S. Bolognesi, D. P.; Hansen, H. J. *J Natl Cancer Inst* 60(1): 139; 1978.

Induction of specific immunity against the AD755a tumor by sc inoculation of C57BL/6J mice with tumor cells was investigated. Syngeneic mice could be immunized against challenge with greater than  $10^4$  times the dose of cells necessary to kill 100% of the mice by sc inoculation of  $10^5 \times 10^5$  cells. The mice were then resistant to further challenges for at least 3 mo. Hyperimmunization by reported sc ip injections of tumor cells resulted in donor mice whose spleen and lymphoid cells could transfer specific immunity to nonimmunized mice. The immune serum could provide protection by transfer of as little as 5  $\mu$  liters; this protection appeared to be strain specific. Protection against Ehrlich ascites carcinoma and sarcoma 180 could also be achieved by this procedure. Transfer of protection could not be achieved by transfer of thymocytes. Preliminary results suggested that the protection was contained in the IgG fraction and had an in vivo half life of  $\geq 4.5$  days. The immune serum also inhibited rosette formation between normal mouse lymphoid cells and the AD755a tumor cells. Possible mechanisms of immune-transferred protection are discussed. Minor histocompatibility differences could be responsible for the tumor immunity described. (28 refs.)

0941 **Reduction of Syngeneic Tumor Growth by an Anti-I-J Alloantiserum.** (Eng) Greene, M. I. (Dept. Pathology, Harvard Medical Sch., 25 Shattuck St., Boston, MA 02115); Dorf, M. E.; Pierres, M.; Benacerraf, B. *Proc Natl Acad Sci USA* 74(11): 5118-5121; 1977.

The effect of batch 480 of (3R x DBA/2) $F_1$  anti-5R antisera (anti-I-Jk) on tumor growth in female A/J (H-2a) mice was investigated. Batch 492 of (3R x 9R) $F_1$  anti-B10.HTT serum containing anti-I-Js antibody was used as a control. Anti-I-Jk serum was administered in vivo (2  $\mu$ l/day iv) at the time of injection of  $10^5$  S1509a cells into nonimmune A/J mice and continued for 15 days. Anti-I-Jk serum reduced tumor growth as early as day 3, and this effect persisted through day 15. The activity of the anti-I-Jk serum was due to its interaction with antigenic determinants coded by the *H-2k* major histocompatibility complex, particularly the *I-Jk* subregion. Administration of 20  $\mu$ l of serum with the same tumor

burden had a more dramatic effect on early tumor growth, but by day 8, the effect was similar. When 2 or 20  $\mu$ l of anti-I-Jk serum were administered with an inoculum of  $10^6$  tumor cells, tumor growth was also decreased, and the effect with each dose was basically the same. The anti-I-Jk-induced decrease in tumor growth was attributed to loss of endogenous suppressor cell activity. Thus, mice that have received this serum cannot be used as a source of exogenous suppressor cells for adoptive transfer into immune mice. Similar effects on growth inhibition were observed with injection of  $10^5$  Sa-I tumor cells into A/J mice followed by 2  $\mu$ l anti-I-Jk serum. (17 refs.)

78-0942 **Inhibition and Promotion of Tumor Growth by BCG: Evidence for Stimulation of Humoral Enhancing Factors by BCG.** (Eng) Ishibashi, T. (Res. Inst. Diseases Chest, Faculty Medicine, Kyushu Univ., Maidashi, Higashiku, Fukuoka, 812 Japan); Yamada, H.; Harada, S.; Harada, Y.; Takamoto, M.; Sugiyama, K. *Int J Cancer* 21(1): 67-71; 1978.

The time-dependent effect of BCG on the growth of transplantable methylcholanthrene-induced fibrosarcomas in C3H/He mice was investigated. BCG (1 mg) was inoculated into a footpad 4, 7, and 11 wk prior to tumor challenge with 20,000 tumor cells in the contralateral footpad. BCG administered 4 and 7 wk previously suppressed tumor growth. Similar BCG inoculations were performed and  $2 \times 10^4$  tumor cells were inoculated into the same footpad. A significant rejection of tumor was observed in mice receiving the BCG 7 and 11 wk before tumor challenge. A repeat of this experiment with a tumor inoculum of  $1 \times 10^5$  cells showed suppression of primary tumor growth with BCG treatment 7 wk before challenge; however, lymph node and lung metastases were noted. Posttreatment with BCG at a site distant to sc injection of  $3 \times 10^5$  tumor cells caused promotion of tumor growth. Enhanced antibody formation and suppression of delayed type hypersensitivity (DTH) occurred in tumor-bearing mice. BCG treatments enhanced antibody formation and suppressed DTH. Sera from tumor-bearing animals enhanced tumor growth when injected ip into mice with sc tumors; splenectomy suppressed tumor growth. It is suggested that antibodies against tumor-specific antigens enhance tumor growth in this system and that BCG stimulates antibody formation in tumor-bearing mice. (22 refs.)

78-0943 **Effects of Prophylactic Treatment with the Methanol Extraction Residue Fraction of Tubercle**



**Bacilli (MER) on the Development of Rous Sarcomas of Chickens Following Challenge with the Rous Sarcoma Virus.** (Eng) Markson, Y. (Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Doljansky, F.; Weiss, D. W. *Isr J Med Sci* 14(1): 51-59; 1978.

The effect of pretreating 3-mo-old White Leghorn chickens with the methanol extraction residue (MER) fraction of tubercle bacilli before viral challenge with  $10^6$  focus-forming units of the Schmidt-Ruppin strain, subgroup A, of Rous sarcoma virus was determined. All 46 chickens treated with 0.5 mg MER 14 and 3 days before viral challenge in the same wing developed tumors, of which 15 regressed. Forty of 42 controls also developed tumors, but none regressed. With only one 0.5 mg treatment 14 days before challenge, 32/32 animals developed tumors and 4 regressed; the respective figures for the controls were 26/28 and 0. MER pretreatment was then administered at the same dose and on the same 2 days but into the contralateral wing. In both treated and control groups, 19/20 animals developed tumors and none regressed. Similar results were obtained with one pretreatment. When the dose of MER was reduced to 0.25 mg and treatment was administered twice to the same wing, 15/16 animals developed tumors and 1 regressed, compared to 16/16 controls with tumors and no regressions. Similar results were obtained with one pretreatment. Thus, one or two pretreatments into the contralateral wing produces no effects on tumor incidence or regression. All experiments were repeated at different times of the year with essentially the same results. Seven birds who had regression of their tumor were rechallenged with virus 38-56 days after the first challenge; no tumor development was noted. Birds given MER but not showing tumor regression survived longer than saline-treated controls. (14 refs.)

**78-0944 Immunologic Surveillance Against Chemically Induced Primary Colon Carcinoma in Rats.** (Eng) Bansal, S. C. (Dept. Surgery, Alma Dea Morani Lab. Surgical Immunobiology, Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129); Mark, R.; Bansal, B. R.; Rhoads, J. E. *J Natl Cancer Inst* 60(3): 667-675; 1978.

The effect of immunosuppression on 1,2-dimethylhydrazine dihydrochloride (DMH)-induced gastrointestinal tract tumors in inbred W/Fu rats was investigated. In preliminary experiments, four groups of rats were exposed to a total of 7-23, 25-33, 30-40, and 45-55 mg DMH for 9-38, 33-70, 71-95, and 112 days, respectively. A 5-wk exposure resulted in few light microscopy-identifiable alterations. However, 53 foci of mucosal changes were present in 11 rats exposed to 45-55 mg DMH for 112 days. Thirty rats were then treated with a total of approx 35.5 mg DMH for 77 days; 10 days later, 18/30 rats received antithymocyte globulin (ATG: 10 mg/kg/day for 4 days). In another experiment, 30 rats received approx 51 mg DMH for 112 days; 10 days later, 18/30

rats received ATG treatment. The numbers of tumors and metastases were higher in both ATG-treated groups than in the ATG-untreated groups. Furthermore, multiple tumors occurred more frequently in the immunosuppressed animals and higher proportions of these tumors were invasive. With the passage of time after the last DMH dose, the number of mucosal abnormalities were comparable. It is concluded that ATG immunosuppression allowed the development of microtumor foci into gross neoplasms. Apparently, immunologic surveillance against neoplasia depends on the thymus cell system, although other mechanisms cannot be excluded. (44 refs.)

**78-0945 Adenocarcinoma of the Small Bowel Complicating Crohn's Disease in a Patient Treated with Azathioprine.** (Eng) Westaby, S. (Addenbrooke's Hosp., Cambridge, England); Everett, W. G.; Dick, A. P. *Clin Oncol* 3(4): 377-381; 1977.

A 49-yr-old woman developed adenocarcinoma of the small bowel 25 yr after diagnosis of Crohn's disease. She had received azathioprine (1.5 mg/kg/day) for the 7 yr prior to admission. The drug's immunosuppressive effects could have allowed developing malignant cells to escape immune surveillance. (19 refs.)

**78-0946 Serum-associated Inhibition of Leukotaxis in Humans with Cancer.** (Eng) Maderazo, E. G. (Medical Res. Div., Dept. Medicine, Hartford Hosp., Hartford, CT, 06115); Anton, T. F.; Ward, P. A. *Clin Immunol Immunopathol* 9(2): 166-176; 1978.

Of 24 human patients with various malignancies, 16 had a reduction in leukotactic function due to the presence of an inhibitor that affected neutrophil and monocyte reactivity and phagocytic ability. This inhibitor could account for the inability of cancer patients to mount cellular inflammatory reactions. (24 refs.)

**78-0947 In Vivo and In Vitro Studies on Nonspecific Blocking Factors of Host Origin in Cancer Patients: Role of Plasma Exchange as an Immunotherapeutic Modality.** (Eng) Israel, L. (Unite de chimio-immunotherapie, Centre Hospitalier Universitaire de Bobigny, Universite Paris Nord, 93000 Bobigny, France); Edelstein, R. *Isr J Med Sci* 14(1): 105-130; 1978.

Experimental and clinical data on elevated glycoprotein levels in tumor-bearing animals and cancer patients are reviewed. Serum protein assays in 232 patients with various solid tumors revealed consistently high levels of  $\alpha_1$ - and  $\alpha_2$ -globulins, including  $\alpha$ -antitrypsin, orosomucoid, ceruloplas-



and haptoglobin.  $\beta$ -Globulins were also increased, but the  $\gamma$ -globulins, only IgA levels were elevated consistently. Of 24 patients with metastatic disease treated by plasmapheresis, 8 exhibited partial tumor regression that may have resulted from the removal of immunosuppressive products. In normal subjects, lymphocyte responses to phytohemagglutinin were inhibited by orosomucoid, haptoglobin, and transferrin. It is suggested that tumors may promote themselves by triggering hepatic synthesis of sialoglycoproteins that coat the binding sites of both immunocompetent cells and tumor cells, thus abrogating recognition and killing of the latter by the immune system. Circulating sialoglycoprotein assays could be one of the ways of monitoring tumor growth, including growth during the nonvisible phase. (113 refs.)

#### 0948 Suppressor Cells and Specific Blocking Factors in Tumor Immunity (Meeting Abstract). (Eng)

Hellstrom, K. E. (Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104); Hellstrom, I. *Fed Proc* 37(3): 486; 1978. (no refs.)

#### 0949 The Lymphoid System of Marmoset Monkeys (*Saguinus Sp.*) and Effects of Immunosuppression (Meeting Abstract). (Eng)

Johnson, D. R. (Univ. Illinois Medical Center, Urbana, IL). *Diss Abstr Int [B]* 38(5): 2044B; 1978. (no refs.)

#### 0950 In Vitro Generation of Suppressor Cells for Transplantation (Meeting Abstract). (Eng)

Clark, J. (Veterans Admin. Hosp., Minneapolis, MN, 55417); Clark, C.; Sigmon, E.; Azar, M. *Fed Proc* 37(3): 559; 1978. (no refs.)

#### 0951 Ultrastructure of Choriocarcinoma Transplanted on Nude Mouse (Meeting Abstract). (Eng)

Wagoe, K. (Dept. Obstetrics and Gynecology, Faculty of Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo, 113, Japan); Yamamoto, S. *J Electron Microsc (Tokyo)* 26(3): 263-264; 1978. (no refs.)

#### 0952 Coincident Effect in the Graft-Versus-Host Reaction of BALB/c Lymphoid Cells Derived from Mice Immune Either to Allogeneic Normal Tissue or Syngeneic Chemically Induced Fibrosarcomata. (Eng)

Imiani, G. (Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan, Italy); Invernizzi, G. *J Immunogenet* 4(3): 177-190; 1977.

The effect of lymphoid cells from BALB/c mice preimmunized to allogeneic tissues on the graft-vs-host reaction (GVHR) induced in hybrids between BALB/c and the immunizing strain was investigated. Lymphocytes from BALB/c mice immune to syngeneic ST2 or ST5 sarcomas performed similarly to BALB/c anti-DBA/2 lymphocytes in increasing the GVHR in (BALB/c x DBA/2) $F_1$  newborns, compared with nonimmune BALB/c cells. This effect was not observed when BALB/c anti-ST2 or anti-ST5 lymphoid cells were given to (BALB/c x C3H) $F_1$  and to (BALB/c x AKR) $F_1$  mice. However, anti-ST2 lymphocytes did increase the GVHR in (BALB/c x C57BL/6) $F_1$  newborns, but anti-ST5 cells had no effect. BALB/c fibrosarcoma C-1 activated syngeneic lymphocytes to increase the GVHR in (BALB/c x C3H) $F_1$  and (BALB/c x AKR) $F_1$  mice but not in other hybrids. These data suggest that chemically induced tumors may express new non-H-2 antigens usually expressed in normal tissues of allogeneic strains and that these antigens have lymphocyte-activating determinants detectable by a GVHR. (27 refs.)

#### 78-0953 In Vitro Retrieval of the Cytotoxic Potential of Spleen Cells of Tumor-bearing Mice. (Eng)

Schechter, B. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Feldman, M. *Isr J Med Sci* 14(1): 131-145; 1978.

Studies of the cell-mediated immune response of C57BL mice to the transplantable syngeneic Lewis lung carcinoma (3LL) are summarized. Although tumor-bearing mice were resistant to a second tumor graft, the in vitro cytotoxicity of their spleen cells declined after 10 days of tumor growth. The decline correlated with an increase in tumor-enhancing cells in the spleen. The in vitro cytotoxicity of the cells could be reactivated by exposure to 3LL cells or by incubation in medium alone. After this reactivation, the cells lost their enhancing activity in vivo and often protected against tumor growth. The possibility that the enhancing cells operated as suppressor cells of antitumor responses was confirmed by the finding that hydrocortisone (HC) inactivated precursors of suppressor lymphocytes. When administered 3-5 days after tumor injection, HC significantly delayed tumor development. Spleen cells from the HC-treated mice were highly protective against tumor cells in vivo, and they were more cytotoxic to tumor cells in vitro than spleen cells from untreated animals. (44 refs.)

#### 78-0954 Tumor Cell Cytotoxicity by Granulocytes from Peripheral Blood of Tumor-bearing Mice. (Eng)

Fisher, B. (Dept. Surgery, Sch. Medicine, Univ. Pittsburgh, 914 Scaife Hall, 3550 Terrace St., Pittsburgh, PA 15261); Saffer, E. A. *J Natl Cancer Inst* 60(3): 687-691; 1978.



Circulating granulocytes from inbred CeHeB/FeJ mice bearing mammary carcinomas exhibited 50% cytotoxicity for the cells from these tumors but only 9% cytotoxicity for the cells from a methylcholanthrene-induced tumor. The mammary tumor-specific cytotoxicity was inhibited by sera from the tumor hosts. Thus, granulocytes may be as important in cell-mediated tumor responses as lymphocytes and macrophages. (24 refs.)

- 78-0955 Enhanced Killer Cell Activities Induced by Progressive Tumor Growth.** (Eng) Lopez, D. M. (Lab. Virology, Dept. Microbiology, Univ. Miami Sch. Medicine, P. O. Box 520875, Biscayne Annex, Miami, FL 33152); Sigel, M. M.; Herbert, L. *J Reticuloendothel Soc* 22(5): 437-443; 1977.

Three different types of cytotoxic activities were studied in syngeneic mammary tumors transplanted in BALB/c mice. Increased reactivities paralleling tumor growth were obtained in phytohemagglutinin-induced cytotoxicity, antibody-dependent cellular cytotoxicity and the recently described specifically induced nonspecifically expressed cytotoxicity. In the last assay, lymphocytes sensitive to a tumor antigen became activated upon confrontation with the antigen and became lytic against unrelated target cells. The increase in these three parameters of cell-mediated immunity with tumor growth is in sharp contrast with previous results obtained in the same model system with the migration inhibition and lymphocyte transformation assays, in which positive reactions disappeared with tumor advancement. These findings indicate that tumor growth has diverse effects on the host's immune system. The contrasting extremes imply that different cell populations are involved, directly or indirectly, in tumor-host interactions and the expression of immunologic responses. (24 refs.)

- 78-0956 Human Spontaneous Killer Cells Selective for Tumour-derived Target Cells.** (Eng) Jondal, M. (Dept. Microbiology and Immunology, UCLA Sch. Medicine, Los Angeles, CA, 90024); Spina, C.; Targan, S. *Nature* 272(5648): 62-64; 1978.

The specificity of human spontaneous killer (SK) cells (a lymphocyte subpopulation that has the capacity to kill certain in vitro propagated cell lines) was examined in the short-term <sup>51</sup>Cr-release assay using a variety of cell lines. All the tumor-derived B-cell lines originated from Burkitt's lymphoma. The T-cell lines were from acute lymphatic leukemia. The K-562 line was derived from chronic myeloid leukemia. Cell lines derived from normal lymphocytes were established either spontaneously or by the addition of transforming Epstein-Barr virus. Cell lines derived from leukemic tumor cells were much more susceptible to spontaneous cytotoxicity than cell lines derived from normal lymphocytes. It is unclear why SK

cells kill tumor-derived target cells more efficiently than normal targets. However, several explanations may be considered: different clones of different sizes of effector cells, qualitative or quantitative difference with regard to surface antigen expression on the target cells, or a difference in general surface characteristics. These results support the proposal that SK cells act in vivo as surveillance cells against tumor development. (19 refs.)

- 78-0957 Specificities of Killing by Cytotoxic Lymphocytes Generated In Vivo and In Vitro to Syngeneic SV40 Transformed Cells.** (Eng) Gooding, L. R. (Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC 27710). *J Immunol* 118(3): 920-927; 1977.

In vivo and in vitro generation of cytotoxic cells at the site of tumor rejection was investigated in freshly derived non-tumorigenic lines of SV-40 transformed cells. T cells were involved in both in vivo and in vitro responses to syngeneic SV40 transformants. In vitro studies suggested that an anti-theta-insensitive effector was involved in the rejection of these transplants. (51 refs.)

- 78-0958 The Role of Lymphocytes in Tumors with Reference to the Phenomenon of Immune Stimulation (Meeting Abstract).** (Eng) Sparck, J. V. (Immunological Lab., State Serum Inst., Copenhagen, Denmark). *Scand J Immunol* 6(11): 1179; 1977. (no refs.)

- 78-0959 Immunologically-induced Focal Lesions in Lymphosarcoma (Meeting Abstract).** (Eng) Grand, N. G. (Dept. Oral Pathology, Div. Surgical Oncology, Univ. Illinois Medical Center, Chicago, IL, 60680); Hakim, A. A. *Fed Proc* 37(3): 932; 1978. (no refs.)

- 78-0960 Lymphocyte Populations Participating in Cellular Antitumor Immune Responses Mediated by Immune RNA.** (Eng) Kern, D. H. (Dept. Surgery, Harbor General Hosp., Torrance, CA 90509); Chow, N.; Pilch, Y. H. *J Natl Cancer Inst* 60(2): 335-344; 1978.

T lymphocytes were found to be intimately involved in cellular antitumor immune reactions mediated by both syngeneic and xenogeneic immune RNA (I-RNA). Syngeneic I-RNA was extracted from unfractionated spleen cell suspension and from various subpopulations of spleen cells from inbred Fischer 344/N rats bearing growing transplants of a 3



ethylcholanthrene-induced sarcoma (3-MC-R) that were incubated separately with nonimmune syngeneic spleen cells, and their cytotoxicity for 3-MC-R target cells was determined. Active I-RNA was extracted from populations of donor lymphoid cells enriched in T lymphocytes. By contrast, I-RNA from cells adherent to RBC-antibody (EA) monolayers (cells) was inactive. The effector cells acted on by the I-RNA also appeared to be T cells. Cells that formed EA rosettes (mostly B cells) showed no increase in cytotoxicity for 3-MC-R target cells, but cells not forming EA rosettes and nonadherent to nylon fiber (mostly T cells) became more cytotoxic after incubation with I-RNA. After incubation with xenogeneic I-RNA extracted from the lymphoid organs of guinea pigs immunized with C3H tumor cells, the cytotoxicity of unfractionated, nonimmune C3H spleen cells for tumor target cells increased. Removal of cells adherent to petri dishes did not change the cytotoxicity, but nonadherent cells were inactive. Exposure to I-RNA increased the cytotoxicity of lymphocytes eluted from nylon fiber columns; however, when these cells were treated with anti- $\theta$  serum and complement, this response was abrogated. Therefore, the effector cells mediating cytotoxic antitumor reactions after treatment with I-RNA appeared to be T lymphocytes. For both syngeneic and xenogeneic I-RNA, the cytotoxic reactions were specific for the tumor used to immunize the I-RNA donors. (55 refs.)

**78-0961 Induction of Immunoregulatory T Cells by Adjuvant.** (Eng) Reinisch, C. L. (Div. Tumor Immunology, Sidney Farber Cancer Inst., Boston, MA 02115). *Am J Med Sci* 14(1): 89-97; 1978.

The effect of adjuvant on suppressor cell generation in the thymus was investigated. C57Bl/6 mice were inoculated ip with complete Freund's adjuvant (CFA), and the capacity of thymocytes and splenic T cells to suppress the in vitro generation of cytolytic T cells was studied. Suppressor thymocytes were detected within 2 days of CFA inoculation, and they preceded the appearance of suppressor T cells in the spleen by 6 days. Characterization of the suppressor thymocyte populations showed that they inhibited primary but not secondary T-cell responses in vitro. It is suggested that the initial step in the regulation of the primary immune response by adjuvant is the generation of suppressor cells in the thymus. Subsequently, thymic suppressors migrate to peripheral lymphoid tissue, where they inhibit cytotoxic, but not helper, T-cell function. (24 refs.)

**78-0962 The Influence of Anti-Theta-Globulin Treatment on the Growth of Mastocytoma in Mice.** (Eng) Syrjanen, K. J. (Dept. Pathology, Jorvi Hosp., 02740 Espoo 74, Finland); Hjelt, L. H. *Exp Pathol (Jena)* 14(3/4): 208-214; 1977.

The growth of a chemically induced mastocytoma (P-815-X2) implanted sc in DBA/2 mice was determined following selective depletion of their thymus-dependent lymphocyte population with anti-theta globulin or anti-thymus globulin. Animals were inoculated sc with 5 mg of the antiglobulin sera at 2-day intervals for four injections. Two days after the last globulin injection,  $10^6$  tumor cells were injected sc. The animals were sacrificed after 2 wk. An increase in tumor growth, indicated by dissemination of the tumor into the spleen, liver, and kidney, was evident in the globulin-treated mice. The death rate and the frequency of thymic metastases were higher in the animals treated with anti-theta globulin than in those treated with anti-thymus globulin. Thus, T-cell activity appears to play an important role in host resistance to experimental neoplasia. (23 refs)

**78-0963 Detection of Metastatic Tumors in Nude Mice: Brief Communication.** (Eng) Graham, S. D. (Div. Urology, Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710); Mickey, D. D.; Paulson, D. F. *J Natl Cancer Inst* 60(3): 715-716; 1978.

Homozygous nude mice were inoculated ip with  $10^7$  cells of malignant human transitional cell bladder carcinoma or prostatic adenocarcinoma. Concomitantly, and weekly thereafter, some of the mice received  $10^6$  normal human T lymphocytes sc or ip. All mice that received T cells had metastatic spread; in those that did not, tumor growth was observed only at the inoculation site. (6 refs)

**78-0964 Kinetics of Thymus- and Bone Marrow-derived Lymphocytes in Rats During Tumor Growth.** (Eng) Klobusicka, M. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Kalafut, F.; Novotna, L. *Neoplasma* 24(6): 583-593; 1977.

The kinetics of T and B lymphocytes were studied in the spleen, lymph nodes, peripheral blood, and thymus of tumor-bearing rats at intervals ranging from 1 to 35 days after transplantation of  $2 \times 10^7$  or  $10^8$  allogeneic MC-1 fibrosarcoma cells. The dose of the transplanted tumor cells was the limiting factor in the altered ratio of T and B cells in the various phases of the immunological response of the tumor-bearing host. Following the lower tumor cell dose, tumor growth was accompanied by a slight depletion of T lymphocytes that returned to normal following tumor rejection (19 days after transplantation). The higher dose of tumor cells caused an evident exhaustion of T cells in all the lymphoid organs, and the tumor was not rejected by the end of the experiment (35 days). B cells were apparently unaffected by transplanted tumor cells. A cell population that could not be identified by the methods used in this study appeared principally in the spleen and lymph nodes of tumor-bearing animals when the



tumor was at its peak and during the process of rejection. These results support the concept that T lymphocytes function as suppressor cells through their participation in the control of tumor growth and that they are responsible for tumor rejection because of their cytotoxic activity. Thus, both subpopulations of T cells ( $T_1$  and  $T_2$ ) participate in the regulatory mechanisms controlling tumor growth and rejection. (38 refs)

**78-0965 Kinetic Study of Carcinogenesis. The Immune Defense and Stability of Tumor Cells. (Fre)**

Garay, R. (Laboratoire de Physiologie et Pharmacologie, I.N.S.E.R.M. U7, Hopital Necker, 75015 Paris, France); Lefever, R. *C R Acad Sci [D] (Paris)* 285(6): 741-744; 1977.

A mathematical kinetic study of three phenomena of carcinogenesis (transformation of a normal cell into a tumor cell, replication of transformed cells, and interaction of transformed cells with the host immune system) is presented. Carcinogenesis showed similarities to first-order phase transitions. Early development of the immune response is necessary for it to have a favorable effect in terms of tumor rejection. (5 refs.)

**78-0966 CLL and Diffuse Histiocytic Lymphoma in One Patient: Clonal Proliferation of Two Different B Cells. (Eng)**

Splinter, T. A. (Dept. Internal Medicine, Univ. Hosp., Wilhelmina Gasthuis, 1e Helmersstraat 104, Amsterdam, Netherlands); Bom-van Noorloos, A.; van Heerde, P. *Scand J Haematol* 20(1): 29-36; 1978.

A combination of chronic lymphocytic leukemia (CLL) and diffuse histiocytic lymphoma (Richter's syndrome) occurred in a 77-yr-old woman who had presented with fatigue, excessive perspiration, and a submandibular tumor. She had been treated in the past for rheumatoid arthritis and spondylosis of the spine. Light microscopy revealed the presence of CLL cells in the blood and bone marrow and a combination of CLL cells and large immunoblastic cells in the enlarged submandibular lymph node. Cell suspensions prepared from the lymph node and blood contained a preponderance of B cells carrying surface immunoglobulin (SIg), but the percentage of rosette-forming cells was below normal. The large immunoblasts, which comprised 65% of the lymph node cells, carried a brightly fluorescing monoclonal membrane Ig  $\mu\kappa$ , but the CLL cells carried a weakly fluorescing monoclonal membrane Ig  $\mu\lambda$ . Both cell suspensions had low stimulatory capacity in mixed lymphocyte culture. It is suggested that the CLL had been present in an asymptomatic form for some time and that it was complicated by the newly developed lymphoma. The cells from both lymphoproliferative diseases were probably two distinct clonal B-cell proliferations. (30 refs)

**78-0967 Myeloid Colony-forming Cells Express Human B Lymphocyte Antigens. (Eng)**

Kaplan, J. (Dept. Pediatrics, Wayne State Univ. Medical Sch., 3901 Beaubien, Detroit, MI, 48201); Inoue, S.; Ottenbreit, M. *Nature* 271(5644): 458-459; 1978.

To determine whether human B lymphocytes and myeloid cells share a common stem-cell precursor, bone marrow cells from four children with acute leukemia or lymphoma in remission were compared for their ability to form macrophage-granulocyte colonies in vitro. The lymphocytes were isolated and depleted of human B-lymphocyte antigens (HLA) and human T-lymphocyte antigens (HTLA). The remaining viable cells were observed for macrophage-granulocyte colonies after 10 days. Compared with control cells preincubated with normal rabbit serum + complement (C), incubation of marrow cells with anti-HLA + C before culture markedly reduced the number of colonies formed on day 10. Incubation of the cells with anti-HTLA, however, increased the number of colonies. Apparently, the myeloid precursor cells capable of forming macrophage-granulocyte colonies express HLA antigens. It is suggested that a stem cell for T, B and myeloid cells expresses HLA antigens that are lost at a prethymic stage of T-cell differentiation. (13 refs)

**78-0968 Association of Autoimmune Diseases with HLA-B8 (Letter to Editor). (Eng)**

von Knorring, J. (Fourth Dept. Medicine, Helsinki Univ. Central Hosp., Helsinki, Finland). *Br Med J* 2(6098): 1354-1355; 1977.

Of 37 patients with polymyalgia rheumatica (PMR), 23 had elevated serum alkaline phosphatase (AP) levels. This rise was associated with increased bile canaliculi activity resulting from pathological structural changes in the walls. Corticosteroid treatment reversed the changes. The alterations could be evidence of subclinical hepatic disease associated with PMR. Although chronic lymphocytic leukemia occurred in a patient 5 yr after onset of PMR, histocompatibility studies have yet to show the involvement of a specific HLA haplotype. The association of HLA-B8 in 54% of a series of patients with PMR and giant-cell arteritis is noted. Cholestatic hepatic dysfunction, but not chronic active hepatitis, has been associated with PMR. (8 refs.)

**78-0969 Genetic Control of Cell-Mediated Responsiveness to an AKR Tumor-associated Antigen**

Mapping of the Locus Involved to the I Region of the H-Complex. (Eng) Meruelo, D. (Div. Immunology, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Deak, B.; McDevitt, H. O. *J Exp Med* 146(5): 1367-1379; 1977.



role of the major histocompatibility complex (H-2) in blocking resistance to murine leukemia viruses was studied by measuring the cell-mediated immune response of F<sub>1</sub> hybrids (between AKR and various C3H and C57BL/10 congenic strains) to an AKR thymoma. The results indicated that the ability to generate a primary or secondary cell-mediated response to an AKR tumor cell antigenic determinant is under H-2-linked control. The locus determining cell-mediated lympholysis responsiveness maps in the I-J region. Nonresponsiveness is associated with the H-2q/k and H-2b/k hybrid genotypes, but responsiveness is associated with the H-2k/k homozygous genotype. Nonresponsiveness may result from dominant suppression, recessive responsiveness, or an alternate mechanism not yet understood. This type of control may be one of several H-2-associated mechanisms against virus-induced neoplasms. (3 refs.)

**70 Interaction of Oncornavirus Proteins with Cell Surface Products of the Major Histocompatibility Complex.** (Eng) Twardzik, D. R. (Viral Oncology Program, NCI, Frederick Cancer Res. Center, Frederick MD 21701); Fowler, A.; Weislow, O.; Hellman, A. *IRCS Med Sci* 5(9): 451; 1977.

Oncofetal surface proteins from BALB/c mice bind to the murine leukemia virus envelope proteins and have characteristics of H-2 and Ia antigens. Major proteins are noted around 45,000 daltons and in the 25,000-35,000-dalton range. These findings suggest that oncofetal proteins can interact with H-2 antigens and form antigen-antibody complexes that are recognized by lymphocytes cytotoxic for infected cells. (3 refs.)

**71 Evidence for an H-2/Viral Protein Complex on the Cell Surface as the Basis for the H-2 Region of Cytotoxicity.** (Eng) Blank, K. J. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY 10461); Lilly, F. *Proc Natl Acad Sci USA* 74(269): 808-809; 1977.

Role of molecules governed by genes in the K and D regions of the H-2 complex in stimulating Friend virus (FV)-induced immune responses was investigated. BALB.B mice immunized with syngeneic FV-induced tumor cells produced lymphocytes with a cytotoxicity for other FV-induced tumor cells that depends only on identity at the H-2D region of the H-2b haplotype. This may be due to the formation of an H-2Db/viral protein complex on the surface of FV-infected cells. (9 refs.)

**72 Polyoma Virus-Human Cell Interactions: Persistence of T-Antigen in Two Cell Lines with**

**and Without Transformation.** (Eng) Takemoto, K. K. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD 20014); Bond, S. B.; Haase, A. T.; Ting, R. C. *J Virol* 25(1): 326-330; 1978.

The interaction of polyoma virus (PyV) and human cells was investigated. Abortive infection, as demonstrated by the synthesis of tumor (T) antigen, was seen in normal fibroblasts, simian virus 40-transformed cells, and a spontaneously transformed skin cell line, but not in normal epithelial cells. In the transformed cell lines, 50%-100% of the cells produced T antigen within 5 days after infection with 100 plaque-forming units of PyV/cell. However, most of the cells lost their antigen-producing capacity upon cell passage, and the cultures were negative by passage 3. All nine fibroblast cell lines had varying degrees of susceptibility to PyV infection, but all became negative for T antigen by passage 4 except two. In one, T antigen persisted in 1%-5% of the cells throughout the lifetime of the culture, but cellular transformation did not occur. In the other, the entire culture became morphologically transformed and eventually consisted of 100% T-antigen-positive cells (Py-B102). The Py-B102 cells did not, however, acquire other transformed characteristics, such as the ability to form colonies in soft agar, to grow in medium containing low serum concentrations, or to induce tumors in nude mice. This is the first time that normal diploid human fibroblast cells have been transformed by PyV. (10 refs.)

**78-0973 Cell-mediated Immune Response to Simian Oncornavirus Antigens in Pregnant Women.** (Eng)

Thiry, L. (Institut Pasteur du Brabant, Rue du Remorqueur 28, 1040 Brussels, Belgium); Sprecher-Goldberger, S.; Bossens, M.; Neuray, F. *J Natl Cancer Inst* 60(3): 527-532; 1978.

Lymphocytes from 69 pregnant women, 34 nonpregnant women (matched to 34 women of the pregnant group for number of previous pregnancies), and 15 women with no history of pregnancy were tested for their responses to mitomycin C-treated cells infected with Mason-Pfizer monkey virus (MPMV), baboon C-type virus, or simian sarcoma virus (SSV). At the end of pregnancy, women who had had five to nine previous pregnancies showed a high frequency (53%) of positive responses to MPMV antigens. The frequencies were 15% for women with fewer pregnancies and 3% for nonpregnant women who also had had five to nine previous pregnancies. Lymphocytes from these nonpregnant women did not respond to baboon C-virus antigens, but positive responses were obtained in 15%-20% of the pregnant women. There was no correlation between responses to MPMV antigens and responses to baboon C-virus antigens. Only 2/48 women (1 pregnant, 1 not) showed a positive lymphocyte response to SSV antigens. The results indicate that two viruses, one related to MPMV and the other to baboon C-virus, may be expressed during pregnancy and induce a transient cell-mediated response. (20 refs.)



- 78-0974 Blood Group Antigens in Adenocarcinoma Foreign to the Host.** (Eng) Levine, P. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021). In: *Cancer Invasion and Metastasis: Biologic Mechanisms and Therapy*. Day, S. B.; Myers, W. P.; Stansly, P.; Garattini, S.; Lewis, M. G.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 5, 517 pp.; 69-73; 1977.

Of the several kinds of RBC antigenic specificities, only the glycosphingolipids play a significant role in adenocarcinoma, and these are the ABO and P blood group systems. The 1951 case of a 66-yr-old woman (group O) with gastric carcinomas whose RBC contained an agglutinin believed to be the first example of a newly discovered blood group system is discussed. She was of the very rare (1:150,000) genotype *pp* [Tj(a-)], or genotype *TjbTjb*, with anti P<sub>1</sub>P<sub>2</sub>Pk (anti-Tja) in her serum (titer 1:4-1:8). Tests of 20 mg of the resected lyophilized tumor showed that it absorbed 16-32 agglutinating units of her own complex of antibodies, of which anti-P<sub>1</sub> was the most important. Thus, the malignancy contained an antigenic determinant foreign to the host or an illegitimate blood group antigen that might have resulted from a mutation. Speculation on the mechanism involved are included. The patient's parents were double first cousins, raising the incidence of genotype *pp* from 1:150,000 to 1:4. Her sister, who had the same genotype, died of uterine carcinoma. The lesions in the uterus and stomach were identical. This is the first pedigree in which the familial malignancy of the patient and her sib was associated with another genetic property, the P system on chromosome 6 (which also carries the histocompatibility antigens). The patient survived for 22 yr without metastases, which may have been prevented by specific immunologic mechanisms. If future studies confirm that mutations involving gene products of the ABO, MN, and P systems result in a specific histologic type of malignancy (ie, adenocarcinomas), the same principle may apply to sarcomas. (8 refs.)

- 78-0975 The Occurrence of a Fetorenal Antigen in Renal Adenocarcinoma.** (Ger) Popelier, G. (Urologische Klinik der Reichsuniversitat Gent, Belgielei 199, B-2000 Antwerp, Belgium); Sion, H. *Urol Int* 32(5): 373-376; 1977.

The occurrence of a fetorenal antigen sharing common antigenic determinants with Australia antigen was investigated in 25 patients with renal adenocarcinomas. This antigen was identified in the renal excretory ducts of human fetuses, and it reacted with the sera of 15/25 patients that had antibodies against Australia antigen. This reactivity was used as the basis of a tumor test for renal tumors as well as a method to understand further the origin of renal adenocarcinomas. Radioimmunoassay of tumor and renal cortex tissue was unsuccessful in detecting the fetorenal antigen in either the water-soluble phase of the homogenate or in the Triton extract of the sediment. The sera of the 15 patients showed no evidence of a renal tumor antibody against Australia antigen.

The existence of the fetorenal antigen may be due to hepatic or liver metastases; antibodies against Australia antigen in the serum of renal carcinoma patients may have originated in the liver. The presence of fetorenal antigen cannot be used as a tumor test. (7 refs)

- 78-0976 Lateral Mobility of Cell-Membrane Antigens in Tumor Cells (Meeting Abstract).** (Eng) Kodama, T. (Lab. Pathology, Cancer Inst., Hokkaido Univ. School of Medicine, Sapporo, Japan); Moriuchi, T.; Kobayashi, H. *Electron Microsc (Tokyo)* 26(3): 239; 1977. (no refs.)

- 78-0977 Soluble Transplantation and Specific Antigens Obtained from the Tumor Cell Surface.** (Russian) Klyuchareva, T. E. (Cancer Res. Center, Moscow, USSR); Deichman, G. I. *Vestn Akad Med Nauk SSSR* (2): 59-60; 1978.

The immunologic activity and specificity of soluble surface antigens obtained from cultures of the simian virus 40 induced tumor E-1 of Syrian hamsters and the spontaneous tumor GT-11 were studied. Tumor cell cultures, which grew in monolayer, were centrifuged and injected ip into Syrian hamsters; 2 wk later, the resistance of the inoculated hamsters was assessed in a transplantation test. Immunization of the hamsters with culture fluid induced antitumor resistance, but immunization with lyophilized fluid stimulated the growth of tumor transplants. (13 refs)

- 78-0978 Immunochemical Studies on Human Cancer. Cancer-associated Antigen Reacting with Antiserum to Stomach Cancer Immune Serum.** (Eng) Furukawa, K. (Dept. Legal Medicine, Sch. Medicine Gunma Univ., Maebashi, Japan); Takizawa, H.; Iseki, S. *Proc Jpn Acad [B]* 53(4): 166; 1977.

An attempt was made to detect the antigen specific to cancer associated with human gastric cancer tissue. Rabbit antiserum immunized with a water-soluble extract of stomach cancer and absorbed with normal human blood plasma and stomach mucosa extract contained a precipitin that reacted with 7/9 gastric cancer extracts. The antiserum also reacted with 2/2 colon cancer extracts, but not with extracts from fetal stomach, intestine, liver and kidney. Therefore, there is a difference between this antigen and carcinoembryonic antigen, which also occurs in colon cancer. The precipitation reaction was inhibited by 0.5 M D-glucosamine and D-galactosamine. The antigenic material produced a single protein band upon polyacrylamide gel electrophoresis, and it was negative upon alcian blue and formazan staining for gly-



n. These results indicate that the antigen consists primarily of protein. It had low carbohydrate and sialic acid contents and showed very slight blood group A activity. The precipitation reaction was also inhibited by urine samples from the gastric cancer patients suggests that the antigen may be excreted via the urine. (10 refs)

79 **Leukocyte Migration in the Presence of Leukemia-Associated Antigen in Down's Syndrome.** Szigeti, R. (Semmelweis Orvostudományi Egyetem, II. Szeklinika, Budapest, Hungary); Revesz, T. *Orv Hetil* 33: 1952-1954; 1977.

Leukocytes from children with Down's syndrome and from normal children showed migration inhibition in the presence of acute lymphocytic leukemia-associated antigen. Acute lymphocytic leukemia-associated antigen caused leukocyte migration inhibition in only 2/3 of the patients and in none of the controls. (24 refs.)

80 **Characterization of an Antigen from the Myelogenous Leukemia Cell Line K-562.** (Eng) Collier, L. L. (Salk Inst., La Jolla, CA 92112); Wust, C. J.; O'Brien, B. B.; Lozzio, C. B. *J Natl Cancer Inst* 59(6): 1667-1677; 1977.

Protein solubilized (by 3 M KCl) from the myelogenous leukemia cell line K-562 specifically inhibited the antibody-dependent, complement-mediated cytotoxicity of  $^{51}\text{Cr}$ -labeled K-562 cells by a monkey antiserum to K-562. When the 3 M KCl extract was fractionated with ammonium sulfate, the specific activity (unit inhibition/mg protein) increased eightfold. Upon polyacrylamide gel electrophoresis (PAGE), this purified fraction migrated as a single protein band with no detectable carbohydrate or lipid. The mol wt of the denatured protein, determined by sodium dodecyl sulfate-PAGE, was 77,000, similar to that of the native protein (70,000) determined by Sephadex exclusion chromatography. The protein was stable at pH 6-8, with an apparent isoelectric point between pH 5 and 6. In addition to being irreversibly denatured at pH 5 or less, it was unstable at osmolarities  $> 0.25$  M (NaCl). It was denatured at temperatures of 50°C or above. Normal human peripheral blood WBC were treated similarly with 3 M KCl and fractionated with ammonium sulfate. Neither the crude preparation nor any fraction purified as described for the specific antigen inhibited the cytotoxicity assay, which indicated at least a quantitative association of the protein on the surfaces of normal WBC. (26 refs.)

81 **Morphological and Biochemical Changes in the Gastric Mucosa of A/HEJ Mice Injected with**

**a Xenogeneic Stomach Antigen.** (Eng) Watanabe, H. (Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima 734, Japan); Hirose, F.; Takizawa, S.; Terada, Y.; Fujii, I. *Acta Pathol Jpn* 27(6): 869-876; 1977.

The glandular stomach of Wistar/Furth rats was homogenized and centrifuged, and the supernatant was used as an antigen to induce atrophic gastritis in A/HeJ mice. The antigen was injected sc (5 mg/protein/0.1 ml) at 1-wk intervals for two administrations. Atrophy of the pyloric gland mucosa was observed 1-2 wk after the final injection; it disappeared at 4 wk, when Alcian blue-PAS-positive cells appeared. Mucous cell proliferation was noted after 8 wk, and adenomatous hyperplasia was observed at 12 mo. In the fundic glands, the parietal cells became pyknotic 1 wk after the final injection; these cells began to decrease after 4 wk. Chief cells decreased slightly. The pH of the gastric fluid increased to as high as 7. The parietal cells were replaced by PAS-Alcian blue-positive cells. The pyloric gland continued to atrophy for 12 mo. After 2 wk, some fundic gland mucosa cells contained a few granules resembling Paneth cells in their cytoplasm. Disaccharidase appeared in the glandular stomach 3 wk after the final injection of antigen. Sucrase activity appeared in the pyloric gland, trehalase or lactase appeared in the fundic gland, and maltase appeared throughout the glandular stomach. Alkaline phosphatase activity was present only in the foveolar epithelium 2 wk after the final injection. (24 refs)

78-0982 **Association of Lymphocyte Alloantigen Genotypes with Levels of Immune Responses.** (Eng)

Gilmour, D. G. (New York Univ. Sch. Medicine, New York, NY 10016); Palladino, M. A.; Scafuri, A. R.; Pollard, L. W.; Benedict, A. A. *Adv Exp Med Biol* 88: 109-120; 1977.

The  $F_2$  progeny from inbred EL6 and EL7 chickens were tested for immune responsiveness in association with *Bu-1* and *Th-1* genotypes (the determining alloantigens for B and T cells, respectively). The EL6 chickens are resistant to Marek's Disease (MD), but the EL7 line has a high incidence of MD following exposure to MD virus. A lower graft-vs-host response (GVH) to major histocompatibility complex (MHC) antigens was associated with the additive expression of *Bu-1a*, which agrees with the lower GVH-inducing ability of EL6 WBC. It appears from these data that *Bu-1a* is associated with a higher activity in the delayed hypersensitivity response to lipid-bovine serum albumin and a lower activity in the T-cell-mediated GVH response. The *Th-1* locus demonstrated a pronounced association with the levels of a 20-day secondary antibody response to the synthetic amino acid copolymer GAT<sup>10</sup>, which took the form of an overdominant genetic action. Response to GAT<sup>10</sup> appears to be controlled by a non-MHC locus. These results are discussed in relation to differences in EL6 and EL7 resistance to oncogenesis, which may be directly dependent upon the surface properties



of these cells. These properties, which may be detected as alloantigens, could influence cell accessibility to malignant transformation by a virus. (24 refs.)

**78-0983 Enhancement of Growth of Allogeneic Mouse Tumor by the IgG<sub>1</sub> Fraction of Alloantibody Preparations.** (Eng) Harris, T. N. (Children's Hosp. Philadelphia, One Children's Center, 34th St. and Civic Center Blvd., Philadelphia, PA 19104); Harris, S.; Henri, E. M.; Farber, M. B. *J Natl Cancer Inst* 60(1): 167-172; 1977.

A comparison of the effects of the original alloantibody preparation and the effects of fractions containing largely IgG<sub>1</sub> antibody was made after transplantation of tumors in allogeneic hosts. Ethanol-fixed *Staphylococcus aureus*, strain Cowan A, was used as an absorbent to prepare IgG<sub>1</sub> fractions of anti-BALB/c alloantibody-containing globulins of the same strain. The IgG<sub>1</sub> fractions of C3H and CBA anti-BALB/c globulins were tested for their effect on the growth of the BALB/c plasmacytomas MOPC-315 and MOPC-460 in C3H and CBA mice by incubation for 30 min at 37 C before transplantation, and by injection of 0.2 ml globulin preparation on the day of tumor implant and every 4 or 5 days thereafter. Anti-BALB/c globulin in its original form had an effect varying from no apparent change to slight enhancement of growth. IgG<sub>1</sub> preparations, however, caused rapid growth of the tumor, doubling the diameter in 4 to 5 days at the max rate of growth. After 15 to 20 days, the tumor size leveled off and decreased until necrotic changes appeared after 4 wk. Normal globulin did not cause an increase in growth over controls. These findings are discussed. (27 refs.)

**78-0984 Receptors for IgM and IgM-Antigen Complex on Human T Lymphocytes Reacting with Specific Anti-human-T-cell Antiserum.** (Eng) Bolhuis, R. L. (Radiotherapy Inst. TNO, 151 Lange Kleiweg, Rijswijk, Netherlands); Nooyen, A. J. *Immunology* 33(5): 679-687; 1977.

The identification of a T lymphocyte receptor that binds IgM antibodies without or after prior complex formation between the antibody and sheep RBC (SRBC) is reported. No prior incubation of freshly isolated peripheral blood lymphocytes was required for the expression of the IgM antibody-binding receptor on T cells. Based on the results of experiments designed for the simultaneous detection of lymphocytes reacting with specific rhodamine-labeled antihuman-T cell antiserum and forming rosettes with EA (early antigen)-IgM complexes of SRBC and the IgM antiserum fraction, the receptor for IgM antibody was demonstrated exclusively on T cells. Preincubation of T cells with free IgM or its Fc fragments led to inhibition of rosette formation with EA-IgM. Treatment of the IgM type pentameric antibody with dithioerythritol to cleave pentameric IgM reduced the percentage

of EA-IgM rosette forming cells (RFC) significantly. The possible significance of this receptor in tumor immunology is discussed. (14 refs.)

**78-0985 Complement-dependent Cytotoxic Antibodies in the Course of Cervical Carcinoma.** (Eng) Christenson, B. (Dept. Virology, Statens Bakteriologisk Laboratorium, S-105 21 Stockholm, Sweden). *Int J Cancer* 20(5): 694-701; 1977.

Complement-dependent cytotoxic antibodies to three cervical carcinoma cell lines (Me-180, SW-732, and HeLa) and to herpes simplex virus type 2 (HSV-2)-infected cells were determined in a longterm study of women with cervical carcinoma. Cytolysis of surface antigens differed significantly between the cervical carcinoma cell lines and HSV-2. Tumor regression during treatment was accompanied by decreasing cytotoxicity in the cervical carcinoma lines, but tumor bearers and patients who became severely ill had high levels of increasing cytotoxic antibodies. The opposite was noted for the antibody response to HSV-2-infected cells: patients with less-advanced cancer had significantly higher cytolytic activity than those who were severely ill and had advanced cancer. Long-term survivors demonstrated high, stable lysis of HSV-2-infected cells. As a control, the cervical carcinoma cell lines, cytolytic activity was tested also in a lung carcinoma cell line, A-549. No significant differences were found between the cervical cancer patients and the control women. Tumor bearers and patients treated for advanced cervical cancer showed a slight but nonsignificant increase in cytolytic activity in the A-549 line. (26 refs.)

**78-0986 Complement-dependent Cytotoxic Antibodies by Interaction with Protein A or Concanavalin A.** (Eng) Larsson, J. J. (Lab. Immunology, NCI, NIH, Public Health Service, U. S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Boyle, M. D.; Borsos, T. *J Natl Cancer Inst* 60(2): 411-418; 1978.

The specific interaction of concanavalin A (Con A) with IgG antibodies and *Staphylococcus aureus* protein A with IgG antibodies was used to study the complement-dependent cytotoxic antibodies produced after the immunization of New Zealand White rabbits with the antigenically distinct guinea pig hepatomas designated line-1 and line-10. Con-A, in the fluid phase or bound covalently to Sepharose 4B, inhibited complement-dependent IgM cytotoxic antibody activity but it had no effect on IgG activity. In contrast, protein A inhibited IgG but not IgM. On the basis of this specificity, the rabbit antisera to line-1 cells consistently proved to be a mixture of IgG and IgM antibodies, whereas the cytotoxic antibody pro-



d against line-10 cells was exclusively IgG, with the ex-  
on of one early bleeding in which some IgM activity was  
stable. However, a comparison of immunization  
ules with line-1 cells demonstrated that, under certain  
itions, cytotoxic antibody could be produced that  
ved essentially like IgM. In all instances the antibody  
predicted on the basis of inhibition with protein A or  
A was confirmed by the behavior of each antiserum in  
fixation of the first component of complement.  
labeled protein A was used to measure the max  
ber of IgG molecules bound to a line-10 cell. This  
was of the order of  $10^6$  molecules/cell. Similar  
ates of the number of cell-bound IgM molecules  
l not be made with  $^{125}\text{I}$ -Con A since unsensitized  
10 and line-1 cells bound approx  $1.1 \times 10^6$  and  
 $10^5$  molecules Con A/cell, respectively. (22 refs.)

0987 **Macrophage-induced Reversal of Immunosup-  
pression by Leukemic Viruses.** (Eng) Specter, S.  
Dept. Microbiology and Immunology, Albert Einstein  
ical Center, Philadelphia, PA 19140; Bendinelli, M.; Ce-  
ski, W. S.; Friedman, H. *Fed Proc* 37(1): 97-101; 1978.

rophages were studied for their role in reversing suppres-  
in two leukemia virus-induced tumor models. In vivo  
ies with Friend leukemia virus (FLV) were unsuccessful  
emonstrating any role for stimulated peritoneal exudate  
cells, which are rich in macrophages, in restoring anti-  
function in leukemic mice. However, in vitro studies  
FLV demonstrated that  $1-3 \times 10^5$  proteose-peptone-  
ulated PE cells from normal syngeneic mice (BALB/c)  
d partially restore immunity when added to  $5 \times 10^4$  FLV-  
ected spleen cells. When the Rowson-Parr virus (RPV)  
el system was used, both PE cells from RPV-infected  
LB/c mice and normal PE cells were capable of restoring  
unocompetence. Neither splenic adherent cells nor lym-  
d cells from other tissues were able to induce recovery  
the immune response when they were added to RPV-  
ected spleen cells. Treatment of PE cells with anti-r-  
sera plus complement had no effect on their ability to  
ore immunity; these findings suggest that macrophages  
responsible for the reversal of immunosuppression. Ap-  
ntly, a balance between macrophage number and activa-  
is required for a normal immune response, especially in  
as of antibody formation by immunologically compo-  
nd splenocytes from leukemia virus-infected mice. (24  
)

0988 **Regional Hyperplastic Lymph Nodes in Breast  
Cancer: The Role of Lymphocytes and Nodal  
Macrophages. An Immunological Study with a Five-Year  
ow-up.** (Eng) Hickok, D. F. (2545 Chicago Ave. S., Min-  
neapolis, MN 55404); Miller, L.; Harris, L. *Surgery* 82(5):  
-715; 1977.

Five Stages I and II breast cancer patients with sinus  
histiocytosis in two or more enlarged regional lymph  
nodes were studied. Peripheral lymphocytes (L), serum,  
and nodal L were tested in vitro for cytotoxicity against  
autologous normal and tumor cells. Nodal macrophages  
were incubated with autologous peripheral L, and  
these activated L were then tested in vitro for cyto-  
toxicity against autologous normal and tumor cells.  
Peripheral L were not cytotoxic to autologous tumor  
cells at ratios of 25:1. Nodal L were specifically cytotoxic to  
autologous tumor cells. Macrophages from hyperplastic re-  
gional lymph nodes transferred tumor-specific immunity to  
peripheral L. Macrophages from small, nonhyperplastic re-  
gional lymph nodes did not transfer tumor-specific immuni-  
ty. All five patients are alive 5 yr after treatment of their  
primary cancer by radical mastectomy. With the advent of  
adjuvant classification and its attack on systemic immunity,  
a quantitative, immunopathological classification of breast  
cancer patients is needed to select patients who might benefit  
from this therapy. (40 refs.)

78-0989 **Macrophage Regulation of the T-Cell Allogene-  
ic Response During Tumor Growth.** (Eng) El-  
gert, K. D. (Dept. Biology, Virginia Polytechnic Inst.,  
Blacksburg, VA 24061); Connolly, K. M. *Cell Immunol*  
35(1): 1-14; 1978.

One-way mixed lymphocyte reactions (MLR) were used to  
determine how in vivo tumor growth affects in vitro macro-  
phage-T-cell interactions. When normal T cells were used,  
reactivity to allogeneic cells required macrophages. The  
nonadherent spleen cell population from week-old tumor-  
bearing mice (TBM) responded without additional macro-  
phages. At all concentrations, addition of exogenous macro-  
phages enhanced the MLR. Macrophage enhancement was  
not contact-dependent nor dependent upon macrophage  
DNA synthesis, but the degree of enhanced activity did de-  
pend on the host stage of tumor development. During initial  
phases of tumor growth, T-cell reactivity was maximally en-  
hanced by the presence of normal or TBM macrophages. In  
the late stages of tumor development, T cells, when exposed  
to macrophages from normal or TBM, exhibited a subnormal  
level of reactivity. Normal T-cell activation by normal macro-  
phages supports theories of T-cell-macrophage synergy. Al-  
though normal in vitro T-cell MLR reactivity was not de-  
pressed by the presence of a 24% macrophage concentration,  
the part macrophages play in T-cell activation and inhibition  
is still unclear. (40 refs.)

78-0990 **A Cytochemical Study on Concanavalin A Bind-  
ing Sites and Their Mobility in Normal and  
SV40 Transformed Human Fibroblasts In Vitro (Meeting  
Abstract).** (Eng) Yokoyama, M. (Dept. Urology, Branch  
Hosp., Faculty Medicine, Univ. Tokyo, Tokyo, Japan). *J*  
*Electron Microsc (Tokyo)* 26(3): 239; 1977. (no refs.)



**78-0991 Suppression of Uptake of Tritiated Thymidine into Tumor and Mitogen-Transformed Cells by Supernatant Fluid of Bone Marrow Cell Suspensions (Meeting Abstract).** (Eng) Dittmer, J. (Boston Univ. Sch. Medicine, Boston, MA, 02118); Corwin, L.; Merluzzi, V. J.; Cooperband, S. R.; Moran, T.; Bennett, M. *Fed Proc* 37(3): 559; 1978. (no refs)

**78-0992 Biosynthesis of the First Component of Complement by Human Fibroblasts.** (Eng) Reid, K. B. (Medical Res. Council Immunochemistry Unit, Univ. Oxford, South Parks Road, Oxford OX1 3QU, England); Solomon, E. *Biochem J* 167(3): 647-660; 1977.

The first component of complement (C1) was synthesized by nine human fibroblast lines, RW, BREN, DUV, EIJO61, IMR90, TO2, WI38, LNSV-40, and HM. Lines derived from Burkitt's lymphoma, cervical carcinoma, rectal adenocarcinoma, neuroblastoma, and B and T cells did not have this activity. Each fibroblast cell synthesized and secreted approx  $1 \times 10^{-4}$  to  $10^{-5}$  effective molecules of C1 in 7-8 days of culture. The behavior of the C1 was identical in most aspects to that of human serum C1, but it was less susceptible to inhibition by rabbit fragment F(ab')<sub>2</sub> anti-(human subcomponent C1q). Addition of 200 µg/ml cycloheximide to the culture media inhibited C1 synthesis; removal of the compound from the media also removed its inhibitory effect. Both the release of C1 hemolytic activity and the incorporation of radioactivity into proteins secreted by the fibroblasts increased linearly un-

til several days after the cultures had reached a state of confluent growth. The radioactivity was incorporated into subcomponents C1q, C1r, and C1s, as judged by the formation of specific immunoprecipitates using antisera against C1r and C1s and by absorption with immune aggregates. The C1q produced had a higher mol wt than that of subcomponent C1q isolated by protein fractionation of fresh serum. Thus, human fibroblast cells synthesize and secrete a hemolytic activity functionally identical in many respects to the C1 hemolytic activity found in human serum. (34 refs.)

**78-0993 Studies on the Complement-derived Chemotactic Factors for Tumor Cells (Meeting Abstract)** (Eng) Orr, W. (Dept. Pathology, Univ. Connecticut Health Center, Farmington, CT, 06032); Varani, J.; Kreutzer, D.; Phan, S.; Senior, R.; Ward, P. A. *Fed Proc* 37(3): 486; 1978 (no refs)

See also:

\*(Rev.): 78-0612, 78-0613, 78-0650, 78-0651, 78-0652, 78-0653, 78-0654, 78-0655, 78-0656, 78-0657

\*(Chem.): 78-0681, 78-0778.

\*(Viral): 78-0840, 78-0844, 78-0854, 78-0861, 78-0871, 78-0873, 78-0885, 78-0886, 78-0887, 78-0892, 78-0893, 78-0897, 78-0908, 78-0912, 78-0913, 78-0914, 78-0922, 78-0923

\*(Path.): 78-0995, 78-1052, 78-1053, 78-1054, 78-1059, 78-1062, 78-1104.



## PATHOGENESIS

**94 Development of Malignant Melanoma on Preexisting Pigment Lesions. Confirmation of Anamnestic Data with the Aid of Patient's Personal Photos.** Paul, E. (Abteilung für klinische und experimentelle Dermatologie, Justus-Liebig-Universität, Gafkystrasse 14, D-3500 Giessen, W. Germany). *Hautarzt* 28(12): 638-647;

anamnestic data of 35 patients with malignant melanoma were confirmed with the aid of the patients' personal photographs. The patients included 28 women and 7 men whose age at the time of tumor excision ranged from 20 to 70 yr. The photographs corroborated statements by the patients that a birthmark had existed prior to the development of the malignant melanoma and that the tumor had developed in uninvolved epidermal tissue. In certain cases, the investigators were able to identify birthmarks on the photographs of the patients prior to their knowledge of the existence of the birthmark. These findings indicate that lentigo malignant melanoma, superficial spreading melanoma, and nodular melanoma may originate from preexisting pigmented spots in uninvolved epidermal tissue. Patients with lentigo malignant melanoma had a long disease history and slow tumor growth, but patients with nodular melanoma had a rapid development of the disease. For cases of superficial spreading melanoma, tumor growth time ranged from a few months to 10 yr. In some cases, however, the photographs indicated much slower tumor development. (24 refs)

**95 Tumor Cell and Host Properties Affecting the Implantation and Survival of Blood-borne Metastatic Variants of B16 Melanoma.** (Eng) Fidler, I. J. (Cancer Res. Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Nicolson, G. L. *Isr J Med Sci* 14(1): 1-10; 1978.

Arrest and survival of low (B16-F1) and high (B16-F10) metastatic variants of B16 melanoma were examined following intravenous injection of the cells into various mice. C57BL/6, Balb/c, and NIH Swiss nude (nu/nu) and their immunocompetent heterozygous littermates (nu/+), and A strain mice were used. When F1 and F10 cells were injected into C57BL/6 mice, most of the tumor cells were immediately arrested in the capillary beds of the lungs; tumor cell death occurred within 24 hr. However, by day 14, F1 and F10 cells had yielded 10 and 269 pulmonary nodules, respectively. When the experiment was repeated with adult thymectomized x-irradiated and sham-thymectomized x-irradiated mice, tumor arrest and survival were always higher in the latter. In both groups of mice, more F10 cells survived in the lungs than F1 cells. When the same number of F1 and F10 cells were injected iv into strain A mice, tumor arrest and survival were lower in these mice than in syngeneic recipients, and

more F10 than F1 cells survived. When F1 and F10 were injected into nu/nu and nu/+ mice, cells from both lines were arrested at higher rates, survived longer, and formed more nodules in the nu/+ mice, suggesting that immunity can affect the arrest and survival of a metastatic tumor. F10 cells had significantly higher rates of arrest and survival in both nu/nu and nu/+ mice than F1 cells. In vitro tumor cell adhesion was studied in organ suspensions from syngeneic C57BL/6, nu/+, and nu/nu mice. No difference in ability to aggregate F1 or F10 cells was noted for any of the three strains. In all cases, lung suspensions were most effective at aggregating tumor cells, and F10 cells were always aggregated at higher rates than F1 cells. (60 refs.)

**78-0996 Skin Tumours in White South Africans. Part III. Distribution of Skin Tumours on the Body.** (Eng) Whiting, D. A. (Dermatology Section, Dept. Internal Medicine, Southwestern Medical Sch., Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235). *S Afr Med J* 53(4): 134-136; 1978.

The distribution of skin tumors in white South Africans was characterized according to body site. Solar keratoses occurred mainly on sun-exposed areas; the multiple keratoses found on covered sites were due to factors other than the sun, such as arsenical poisoning. Cutaneous horns, keratoacanthomas, Bowen's disease, and squamous and basal cell carcinomas were found predominantly on sun-exposed areas. However, 25% of Bowen's squamous carcinomas in situ occurred on covered areas, compared to 4% of squamous cell carcinomas. Over 50% of the superficial basal cell carcinomas arose on covered areas, as opposed to 8% of the nodular basal cell carcinomas. Seborrheic keratoses, intradermal and compound nevi, hemangiomas, and lentigines usually occurred on the face and in women. Histiocytomas, which were also more common in women, were located mainly on the legs; this suggests minor trauma or insect bites as causative factors. Approx 28% of all malignant melanomas occurred on the trunk; all cases of lentigo maligna occurred on exposed areas. On white skin, active junctional or compound nevi may cause melanoma on the trunk; on exposed areas, sunlight can induce melanoma in normal skin or in a lentigo maligna. Nevroid seborrheic keratoses predominated in the inguinal folds and on the penis; these tumors must be distinguished from condyloma acuminatum, which may occur in the same area. (13 refs)

**78-0997 Malignant Hemangioendothelioma: Its Ultrastructure and Alkaline Phosphatase Activity.** (Jpn) Hori, Y. (Dept. Dermatology, Sch. Medicine, Kitasato Univ., Sagami-hara-shi, Kanagawa Prefecture 228, Japan);



Miyazawa, S. *Nippon Rinsho Denshi Kenbikyō* 10(3/4): 223-233; 1977.

The occurrence of cutaneous malignant hemangioendotheliomas in a 76-yr-old woman and a 77-yr-old man is reported. In both patients, the appearance of telangiectatic and edematous plaques was followed by the development of black nodules that ultimately showed bleeding and ulceration. Ultrastructurally, the initial stage of the disease was characterized by swelling of the blood-vessel endothelial cells and narrowing of the vascular lumen. At the end stage, spindle-shaped cells proliferated as bundles forming clefts and spaces; some atypical, cuboidal endothelial cells with indented nuclei were seen between the spindle-shaped cells. Alkaline phosphatase reaction products appeared on the membranes of the former, but not on the atypical endothelial cells. (10 refs)

**78-0998 Polycythaemia Vera -- Transformation to Myelofibrosis and Subsequent Reversal.** (Eng)

Pettit, J. E. (Univ. Otago Medical Sch., P.O. Box 913, Dunedin, New Zealand); Lewis, S. M.; Goolden, A. W. *Scand J Haematol* 20(1): 63-69; 1978.

A 67-yr-old woman developed polycythemia vera (PV) 21 yr ago, and since then, the disease has undergone transformation to myelofibrosis and a subsequent reversal to PV. She was initially treated with pyrimethamine and then for 10 yr with repeated venesections. Following transformation of the disease to myelofibrosis 14 yr after the diagnosis of PV, she was treated with splenic irradiation (2,000 rads in 15 fractions over 21 days) and later with busulphan and melphalan. During the past year, transformation back to PV occurred. Although the part played by therapy in the transformation back to PV is unknown, the splenic irradiation may have been involved. (16 refs)

**78-0999 Four Cases of Malignant Sebaceous Tumors of the Skin-- Histogenetic Consideration and Review of the Literature in Japan.** (Jpn)

Setoyama, M. (Dept. Dermatology, Sch. Medicine, Kagoshima Univ., Usukumachi, Kagoshima 890, Japan); Tanaka, S. *Nishinippon Hinyokika* 39(6): 868-879; 1977.

Four cases of malignant sebaceous tumors originating in the skin are presented. According to the Rulon and Helwig classification, two tumors (in women aged 54 and 67 yr, respectively) were basal cell carcinomas with sebaceous differentiation and the others (in a 53-yr-old man and a 67-yr-old woman) were sebaceous carcinomas. All tumors showed raised lesions on the skin of the face and scalp, and they measured 1.0-3.0 cm in diameter. Histologically, the basal cell carcinomas with sebaceous differentiation were composed of foam cells and immature cells possessing a basophilic cytoplasm. The sebaceous carcinomas comprised foam

cells and immature cells with an acidophilic cytoplasm. Based on the basophilism of the cytoplasm, both tumor types can be differentiated. The histogenesis and clinicopathological nature of sebaceous tumors are discussed. (20 refs)

**78-1000 Ultrastructure of Mucoepidermoid Carcinoma (Meeting Abstract).** (Eng) Chen, S. Y. (Temple Univ., Philadelphia, PA). *J Dent Res* 57(A): 333; 1978. (refs)

**78-1001 Light-Electron Microscopic and Cytochemical Studies on the Morphogenesis of Familial Medullary Thyroid Carcinoma.** (Eng) Schurch, W. (Dept. Pathology, Univ. Maryland, 31 S. Greene St., Baltimore, MD 21201); Babai, F.; Boivin, Y.; Verdy, M. *Virchows Arch [Cell Mol Biol]* 376(1): 29-46; 1977.

Familial medullary thyroid carcinoma (MTC) was investigated in four men and two women aged 19-43 yr. The MTC nodules were bilateral in five and multiple in four of the patients. Except for one patient, they were circumscribed as round or oval in configuration. Light microscopy revealed multifocal C-cell proliferation in five patients. These nodules were mostly limited to the thyroid follicles, but occasionally they extended across the follicular capsule, forming microscopic MTC. Electron microscopy revealed that in some follicles, the proliferating C cells were still covered by a continuous layer of follicular cells, but in others the proliferation extended to the follicular center. C cells were in direct contact with colloid, and ultramicroinvasion of the follicular capsule was detected. Ultracytochemical studies revealed that C cells were localized between follicular cells as well as between follicular cells and the basal lamina of the capsule. The number of secretory granules varied from cell to cell within the nodules, and the malignant cells contained polysaccharides and/or glycoproteins. These observations are consistent with the hypothesis that familial MTC begins as a multifocal C-cell proliferation, limited at first to thyroid follicles, between the capsule and the follicular epithelium. Proliferation extends to the follicular center, and C cells come in contact with the colloid, forming the in situ stage of the carcinoma. Neoplastic cells then invade the follicular capsule and MTC appears. If a dysplastic or benign process precedes the development of malignancy, it cannot be identified with certainty. Amyloid, which is associated with tumor necrosis, was present in the large MTC, but it was not evident in small MTC and within the foci of C-cell proliferation. (41 refs.)

**78-1002 Inherited Medullary Thyroid Carcinoma: A Familial Monoclonal Mutation in One of Multiple Clones of Susceptible Cells.** (Eng) Baylin, S. B. (Oncology



ter, Johns Hopkins Sch. Medicine, Baltimore, MD, 1955); Hsu, S. H.; Gann, D. S.; Smallridge, R. C.; Wells, J. *Science* 199(4329): 429-431; 1978.

origin of inherited medullary thyroid carcinoma was investigated in four black women who were mosaic in normal cells for glucose-6-phosphate dehydrogenase (G6PD) types A and B. Each individual had several tumors that contained A or B. It is suggested that the inherited defect is an allelic mutation producing multiple clones of defective cells. Multiple cells of the developing neural crest containing both A and B G6PD may inherit the initial mutation that makes them susceptible to neoplastic change. Each thyroid tumor subsequently arises must originate from a single or very small clone of the genetically susceptible cells. This chain of events could work in other tumors, such as trichioepitheliomas and neurofibromas. (14 refs)

**78-1003 Squamous Cell Carcinoma of the Thyroid: A Report of Two Cases.** (Eng) Kampsen, E. B. (Dept. Surgery, Univ. Louisville Sch. Medicine, Health Sciences Center, Louisville, KY 40201); Jager, N.; Max, M. H. *J Surg Oncol* 9(6): 567-578; 1977.

Case histories of two women, aged 73 and 59, with squamous cell carcinoma of the thyroid are presented, and the origin of the tumor is discussed. Squamous metaplasia is thought to be the most likely etiology, although occasional adenomas may be derived from embryonic remnants. However, evidence indicating that squamous metaplasia predisposes to squamous cell carcinoma is lacking. Metastases and direct extension of the tumor are more frequent than primary involvement, and a primary tumor may not be found at autopsy. Because of the fulminating course of this lesion, radical surgery offers the best chance of cure. (21 refs.)

**78-1004 Oncocytoma of the Parotid Gland with Malignant Change.** (Eng) Chu, W. (Dept. Surgery, American Oncologic Hosp., Central and Shelmire Ave., Philadelphia, PA, 19111); Strawitz, J. G. *Arch Surg* 113(3): 319; 1978.

Case report of a 68-yr-old man with an oncocytoma of the right parotid gland is presented. Histologic examination showed no invasion outside the capsule, but the cellular morphology and fibrous stromal reaction suggested a preinvasive type of malignant change. (11 refs)

**78-1005 Transitional Cell Tumor of the Pituitary Gland Developing from a Rathke's Cleft Cyst.** (Eng)

Kepes, J. J. (Dept. Pathology, Univ. Kansas Medical Center, Kansas City, KS, 66103). *Cancer* 41(1): 337-343; 1978.

Autopsy of a 79-yr-old diabetic woman revealed a pituitary tumor that developed from the wall of Rathke's cleft cysts. Since the cells corresponded to an early developmental stage of pituitary anterior lobe, it is suggested that this tumor be characterized as a transitional cell tumor of the pituitary. (41 refs)

**78-1006 Multifocal Nondisseminated Neuroblastoma. Report of Two Cases in Siblings.** (Eng) Leape, L. L. (171 Harrison Ave., Boston, MA, 02111); Lowman, J. T.; Loveland, G. C. *J Pediatr* 92(1): 75-77; 1978.

Two siblings, aged 6 mo and 4.5 yr at first admission, developed multifocal nondisseminated neuroblastomas. Six tumors were eventually removed from the former and three from the latter; both are free of disease and without metastases 4.5 yr after the last surgery. Neither of the parents had evidence of neuroblastoma or abnormal catecholamine excretion. (2 refs)

**78-1007 Morbidity of Childhood Neurofibromatosis in Individuals Born To Affected Mothers (Meeting Abstract).** (Eng) Miller, M. (Children's Orthopedic Hosp., Seattle, WA); Hall, J. G. *Clin Res* 26(2): 177A; 1978. (no refs)

**78-1008 Lumbar Myelography: Coincidence of Disk Prolapse and Intradural Tumor.** (Ger) Sartor, K. (Strahlendiagnostische Abteilung, Allgemeines Krankenhaus Altona, Paul-Ehrlich-Strasse 1, D-2000 Hamburg 50, W. Germany); Weber, K.; Fliehdner, E. *Fortschr Geb Roentgenstr Nuklearmed* 128(2): 183-184; 1978.

Lumbar disk prolapse and intradural neurinoma occurred simultaneously in a 59-yr-old man and a 68-yr-old woman. This phenomenon is observed in 1/100 cases of lumbar disk prolapse. Lumbar myelography was effective in demonstrating the upper lumbar region and the lower thoracic regions, and, thus, in identifying the tumor. (1 ref.)

**78-1009 Mesectodermal Leiomyosarcoma of the Antrum and Orbit.** (Eng) Jakobiec, F. A. (Edward S. Harkness Eye Inst., Box 57, New York, NY 10032); Mitchell, J. P.; Chauhan, P. M.; Iwamoto, T. *Am J Ophthalmol* 85(1): 51-57; 1978.

A 39-yr-old man developed a left antral leiomyosarcoma



that subsequently spread to the ipsilateral orbit. The tumor had the light microscopic appearance of a malignant schwannoma, but ultrastructural studies demonstrated its derivation from smooth muscle. The atypical neural appearance probably reflected the neural crest contribution to the cephalic connective tissues. (15 refs.)

- 78-1010 Pulmonary Neoplasms and Past Diseases.** (Pol) Biesiekierska-Chanko, I. (Klinika Gruzlicy i Chorob Pluc AM, 80-217 Gdansk, Poland). *Wiad Lek* 30(20): 1593-1597; 1977.

Study of past infections and other diseases in 149 patients with malignant lung tumors and 146 patients with pulmonary tuberculosis revealed past infections and other diseases in 64.38% of the tuberculosis patients and 30.2% of the tumor patients. (14 refs)

- 78-1011 Carcinoma of the Nasopharynx in the Young. Clinical, Pathological, and Ultrastructural Study of 50 Cases in Eastern Algeria.** (Fre) Lemaigre, G. (Service Central d'Anatomie et de Cytologie Pathologiques, Hopital Cochin, 27, rue du Faubourg Saint-Jacques, F 75014, Paris); Diebold, J.; Temmim, L.; Arseniev, I.; Lecharpentier, Y.; Allouache, A.; Delaitre, B.; Abelanet, R. *Nouv Presse Med* 6(38): 3509-3513; 1977.

Fifty cases of nasopharyngeal cancer were diagnosed by biopsy of the primary tumor in 25 (12 with lymph node biopsy) and of the lymph node alone in 25. The age range of the 50 patients was 9-67 yr but the highest number were aged 15-25 yr. In Africa, particularly North Africa, the prevalence of this carcinoma is high in young subjects. (20 refs.)

- 78-1012 Multiple Glomus Tumors.** (Eng) Pepper, M. C. (Section Dermatology, Dept. Medicine, Univ. Chicago Pritzker Sch. Medicine, 950 E. 59th St., Chicago, IL 60637); Laubenheimer, R.; Cripps, D. J. *J Cutan Pathol* 4(5): 244-257; 1977.

Case histories are presented for a father and son having multiple glomus tumors. The father had widespread, slowly evolving vascular lesions since infancy suggestive of the blue rubber bleb nevus syndrome. His 11-yr-old son had two painless lesions typical of multiple glomus tumors. Many of the man's nodular lesions were painful and had been excised but post-excision recurrences were seen. Histologic studies of asymptomatic tumors from both cases showed irregular, dilated, vascular channels surrounded by narrow mantles of glomus cells, whereas a painful tumor had large foci of glomus cells with wider mantles around the flattened channels. Electron

microscopy indicated that the glomus cells were modified smooth muscle cells. It is important to differentiate the essentially benign multiple glomus tumors from the morphologically similar blue rubber bleb nevus syndrome which is associated with a definite morbidity because of the fragility of the mucosal lesions. Multiple glomus tumors may be derived from simple cutaneous vessels instead of the Sucquet-Hoy canal of the normal cutaneous glomus body as previously suggested. Such derivation of multiple tumors from cutaneous vessels could account for the earlier age of onset and the widespread distribution, in marked contrast to the adult onset and acral distribution, of solitary glomus tumors. (43 refs)

- 78-1013 Giant Cell Tumor of Tendon Sheath and Pigmented Villonodular Synovitis: An Ultrastructural Study.** (Eng) Alguacil-Garcia, A. (Dept. Surgical Pathology, Mayo Clinic, 200 First St. SW, Rochester, MN 55901); Unni, K. K.; Goellner, J. R. *Am J Clin Pathol* 69(6): 6-17; 1978.

Light and electron microscopic observations of five giant cell tumors of the tendon sheaths of the palm and one type II pigmented villonodular synovitis of the knee are presented. Light microscopically, the giant cell tumors had abundant plump and oval histiocytic-appearing cells with varying proportions of spindle cells, foam cells, and benign multinucleated giant cells. The synovitis showed hypertrophied synovial cells with occasional mitotic figures. Ultrastructurally, the giant cell tumors were composed mainly of A- and B-type synovial cells. Fibroblastic cells and monocytic and lymphocytic cells were also present. The giant cells appeared to be derived from the fusion of synovial A-type cells, the foam cells from B-type A and B cells. Both the giant cell tumors and the pigmented synovitis are considered to be reactive and borderline neoplastic proliferative lesions of the synovial cells. (44 refs)

- 78-1014 Giant Cell Tumors of Tendon Sheath. An Electron Microscopical Study of 11 Cases.** (Eng) Carstens, P. H. (Dept. Pathology, Univ. Louisville School of Medicine, Louisville, KY, 40201). *Arch Pathol Lab Med* 102(2): 99-103; 1978.

Eleven giant cell tumors of the tendon sheaths of the hand which occurred in six men and five women aged 19-73 years were studied electron microscopically. Observations for all tumors were essentially the same. The giant cells had many similarities to normal osteoclasts. However, three specimens had cytoplasmic crystals consisting of straight-running filaments with a periodicity of approx 80-100 Å. They were often found with a structureless electron-dense material; the nature of these crystals is unknown. There were four types of stromal cells: osteoblast-, mesenchymal-, fibroblast-, and histiocytic-like. The similarities between the stromal cells and their teogenic counterparts were not as striking as those between



cells and normal osteoclasts. Cytoplasmic crystals similar to those in giant cells were seen occasionally. The tumors were rich in vascular structures and sinusoids. Areas of osseous and mineralized matrix were found in tissues from two patients. It is suggested that these tumors are derived from mesenchymal cells with partial osseous differentiation. (14 refs)

**78-1015 Histochemical and Electron Microscopic Studies of Proliferation of Connective Tissue in Gastric Carcinoma. Part 1: Special Reference to the Stromal Reaction Related to the Spreading Mode of Gastric Carcinoma.** (Jpn) Hanabusa, N. (First Dept. Surgery, Okayama Univ. Medical Sch., Shikada-cho, Okayama 700, Japan). *Yamaguchi Igaku Zasshi* 89(9/10): 1049-1067; 1977.

Immunohistochemical reactions, classified as fibrous stromal defense and cellular stromal defense, were studied in 102 advanced gastric carcinomas. The fibrous stromal defense was examined in relation to connective tissue proliferation. Structures such as blast sheaths encircling the gastric gland were always present in the well-differentiated adenocarcinomas, but were not seen in the poorly differentiated adenocarcinoma because of the failure of glandular formation (signet ring cell carcinoma). Connective tissue proliferation was excessive in the poorly differentiated adenocarcinomas because of the regression or absence of basement membrane. The proliferation indicated formation of collagen fibers and mucopolysaccharides. It is suggested that the interaction between the tumor cell and pericancerous connective tissue is an important factor in the spread of gastric carcinoma. (57 refs)

**78-1016 Correlation of Gastric Cancer and Atrophic Border.** (Jpn) Kawahara, K. (First Dept. Internal Medicine, Yamaguchi Univ., Sch. Medicine, Ube-shi, Yamaguchi Prefecture 755, Japan); Okazaki, Y.; Iida, Y.; Iwaki, N.; Kawamura, S.; Nakamura, K.; Takemoto, T. *Gastroenterol Endosc* 19(9): 953-959; 1977.

The site of origin of 117 early gastric cancers was studied by endoscopy and the Congo red method. Seventy-six percent of the early cancers developed in the pyloric gland area, 18% in the glandular border area, and 3.6% in the fundic gland area. The endoscopic atrophic border shifted from the O-II to the O-III type, depending on age. Macroscopically, 76% of the 41 elevated tumors were differentiated adenocarcinomas that were located primarily in the pyloric gland area. Histologically, 10/10 fundic gland tumors were undifferentiated and 73/83 pyloric gland tumors were differentiated. Of the 18 cancers in the glandular border area, 15 were undifferentiated type. (9 refs)

**78-1017 Enterokinase Activity in Human Intestinalized Gastric Mucosa.** (Eng) Simon, L. (Dept. Gas-

troenterology, Hosp. Jaszbereny, Jaszbereny H-5101, Hungary); Figus, A. I. *Digestion* 16(1/2): 48-50; 1977.

Enterokinase activity in the gastric mucosa was investigated in biopsy specimens from six patients with extended intestinal metaplasia of the gastric mucosa. These patients had a lower amount of enterokinase activity than normal volunteers, but their activity could be increased significantly by 1 mg glucagon iv. Thus, intestinal-type brush border gastric mucosa cells have the same absorptive and secretory properties as their intestinal counterparts. (9 refs)

**78-1018 Gastric and Duodenal Lesions Associated with Familial Polyposis Coli.** (Jpn) Uahio, K. (Dept. Diagnostic Radiology, Natl. Cancer Center, Chuo-ku, Tokyo 104, Japan); Abe, S.; Mitsushima, T.; Kimura, T.; Moriyama, N.; Takasugin, T.; Okazaki, M.; Matsue, H.; Sasagawa, M.; Yamada, T.; Koguro, Y.; Kohei, S.; Hojo, K.; Koyama, Y.; Itabashi, M.; Hirota, E.; Ichikawa, H. *Stomach Intestine* 12(11): 1547-1557; 1977.

Stomach, duodenal, bone, and other lesions were examined in 30 subjects from 14 pedigrees with familial polyposis coli not accompanied by distinct masses. Gastric polypoid lesions were observed in 17/27 cases. These lesions were classified into two groups: fundic glandular lesions showing localized simple hypertrophic change and pyloric glandular lesions showing atypical epithelium. Flat polypoid lesions of the duodenum were observed in 12/13 cases, and adenomas were found in 9. Small osseous abnormalities, such as osteoma, exostosis, and cortical thickening were present in 11/22 patients. Orthopantomography revealed multiple osteosclerotic lesions of the mandible and maxilla in 20/23 subjects. Teeth abnormalities were common. Epidermal cysts were found in three cases and there was one case each of gastric cancer, thyroid cancer, adrenal adenoma, and mesenteric desmoid tumor. The cases accompanied by osseous changes (Gardner's syndrome) and those without them (familial polyposis coli) did not differ with respect to the number and size of polyps in the large intestine, duodenum, stomach, or other lesions. Therefore, these two entities are the same systemic disease with a predisposition to multiple tumor formation, and they both should be called familial gastrointestinal polyposis syndrome. (37 refs)

**78-1019 Familial Polyposis of the Colon.** (Pol) Szklanny, J. (Klinika Chirurgie Ogólnej, Instytut Chirurgii AM, ul. Obornicka 17/50, Lodz, Poland); Zaloga, K.; Kun, M.; Modzelewski, B. *Przegl Lek* 34(12): 877-879; 1977.

Polyposis of the colon was found in two sisters and one brother of a man with glandular polyps of the colon. The son of a third sister, the patient's father, and an uncle on the father's side probably have polyposis. Polyposis is suspected in the



paternal grandfather, another son, and the daughter of his daughter. (5 refs)

- 78-1020 Cancer in Crohn's Disease after Diversionary Surgery. A Report of Seven Carcinomas Occurring in Excluded Bowel.** (Eng) Greenstein, A. J. (Dept. Surgery, Mount Sinai Sch. Medicine, Fifth Ave. and 100th St., New York, NY, 10029); Sachar, D.; Pucillo, A.; Kreel, I.; Geller, S.; Janowitz, H. D.; Aufses, A. *Am J Surg* 135(1): 86-90; 1978.

Seven intestinal cancers occurred in 132 patients who had undergone previous bypass surgery for Crohn's disease. All seven cancers occurred in excluded loops: four in the small bowel and three in the colon. The average latent period between bypass and development of cancer was 13 yr. (26 refs)

- 78-1021 Small-Bowel Malabsorption and Gastrointestinal Malignancy.** (Eng) Collins, S. M. (Dept. Medicine, McMaster Univ. Medical Centre, Hamilton, Ontario, Canada); Hamilton, J. D.; Lewis, T. D.; Laufer, I. *Radiology* 126(3): 603-609; 1978.

Case histories are presented for four patients with malabsorption due to celiac disease who were found to have a malignant tumor of the gastrointestinal tract, and the literature on the subject is reviewed. Of the four patients, one had lymphoma and the other three had cancer of the esophagus, jejunum, and pancreas, respectively. The onset of gastrointestinal malignancy was frequently associated with a loss of response to gluten withdrawal. One of the patients regained sensitivity to gluten withdrawal after resection of in situ carcinoma of the jejunum. A rising level of serum IgA was associated with the development of lymphoma. The literature indicates that carcinoma of the esophagus and small bowel is particularly common in patients with celiac disease. Tumors have also been reported in the stomach, colon, tongue, and pharynx. These findings suggest that celiac disease should be considered a premalignant condition. (34 refs)

- 78-1022 Ultrastructure of the 'Transitional' Mucosa Adjacent to Large Bowel Carcinoma.** (Eng) Riddell, R. H. (Dept. Pathology, Univ. Chicago Hosps. and Clinics, 950 E. 59th St., Chicago, IL 60637); Levin, B. *Cancer* 49(5, Suppl): 2509-2522; 1977.

Thirteen specimens of mucosa adjacent to the large bowel carcinoma were examined by scanning (SEM) and transmission electron microscopy (TEM) and light microscopy (LM). LM indicated that the transitional mucosa was thicker than the mucosa at the resected margin. There was an increase in the size and number of cells and nuclei, and goblet cells were

also numerous and enlarged. Sulfomucins were absent or scarce, so that the entire mucosa consisted of sialomucin only. According to TEM, the base of the crypts had immature cells, but numerous mature goblet cells were present. There was a differential rate of maturation in the upper part of the crypt. There was also a tendency for cells to be shed into the lumen of the crypt at an early stage of development. The superficial epithelium was irregular, with marked vacuolation of the cells about to be shed. Mitochondria and lysosomes were numerous. SEM showed no abnormalities in the transitional zone in 4/13 specimens; the remainder showed major abnormalities. The most striking change was the loss of normal structure, ranging from mild distortion and loss of normal primary crypt arrangements to marked distortion and replacement of the crypt arrangements by a series of irregular nodules. The secondary crypt structure (crypts of Lieberkuhn) was also lost, but crypt orifices were noted between the nodules. These secondary crypts had various degrees of disorganization: some were incomplete or surrounded by an incomplete whorl of cells, and in some there was almost total destruction of the architecture, resulting in a villous appearance. The importance of these findings in the identification of patients at risk for colon cancer is discussed. (16 refs.)

- 78-1023 Tritiated Thymidine Incorporation into Epithelial Cells of Normal-appearing Colorectal Mucosa of Cancer Patients.** (Eng) Maskens, A. P. (Service d'Anatomie Pathologique, Hopital Universitaire St. Pierre, B-3000, Louvain, Belgium); Deschner, E. E. *J Natl Cancer Inst* 58(5): 1221-1224; 1977.

A radioautographic analysis of the number and position of labeled epithelial nuclei after in vitro  $^3\text{H}$  incorporation was made with 30 specimens of histologically normal colorectal mucosa from 13 patients with rectal or sigmoid cancer and 13 controls. The mean labeling index was 9.8% in the cancer group and 7.9% in the control group. Because of wide individual variations, this difference was not statistically significant. However, a highly significant upward shift of the proliferating cell compartment in the cancer group resulted in a specific modification of the  $^3\text{H}$  labeling pattern in 10 specimens. DNA synthesis predominated in the middle and upper thirds of the crypts of Lieberkuhn rather than in the lower third, as observed in the controls. The patchy activation of epithelial cell renewal in colorectal cancer is suggestive of a defect in the regulatory control mechanism. The in vitro  $^3\text{H}$ -incorporation assay may be useful in identifying high-risk populations. (20 refs.)

- 78-1024 Urinary Glycosaminoglycan Patterns in Hepatic Carcinoma of the Liver.** (Eng) Curran, K. (Cancer Center, Univ. Louisville, Louisville, KY 40202).



chella, C. E.; Tamburro, C. H. *Cancer* 40(6): 3050-3053;

urinary chondroitin sulfate fraction was examined in a 40-yr-old man with advanced hepatic angiosarcoma who had been in a vinyl chloride plant for 13 yr, a 54-yr-old man with moderately advanced hepatic angiosarcoma who had been in a vinyl chloride plant for 28 yr, and two normal controls. The specimens were separated into hyaluronic acid, chondroitin sulfate, and heparin fractions. Anion exchange chromatography of the hyaluronic acid and heparin fractions revealed no qualitative differences between controls and patients. The chondroitin sulfate fraction of the patients had an increased total amount of uronic acid in a hyaluronidase-resistant fraction and a decreased amount in a fraction susceptible to hyaluronidase digestion. These changes appeared to become more pronounced with advancing disease. The resistant fraction was heparin sulfate and the susceptible fraction was either chondroitin-4-sulfate and/or chondroitin-6-sulfate. These tests could be useful in the detection of vinyl chloride-induced liver disease. (22 refs.)

78-1025 **Invasion of Liver Tissue by Tumor Cells and Leukocytes: Comparative Ultrastructure.** (Eng) Lemmans, K. P. (Lab. Pathological Anatomy, Wilhelmina Hospital, Eerste Helmersstraat 104, Amsterdam, Netherlands); Roos, E.; van den Bergh Weerman, M. A.; van der Hart, I. V. *J Natl Cancer Inst* 60(3): 583-598; 1978.

Approx 10<sup>6</sup> cells from a spontaneous lymphosarcoma of a BL x DBA/F<sub>1</sub> mouse were injected into the portal system of isologous mice. Invasion of liver tissue by the lymphosarcoma cells and monocytes, especially the mode of penetration of the sinusoidal endothelium, was studied ultrastructurally by serial sectioning of host tissue. Comparative analysis showed that the behavior of these two cell types was similar despite some quantitative differences. Both cell types initiated invasion by extending large numbers of thin processes, apparently located randomly over their surfaces. Although many of these processes completely traversed the endothelium, others merely indented its surface, which indicated that the site of extension of cell processes is not necessarily at preexisting fenestrations. In addition, gaps were found that were not associated with these cell processes. Gaps completely through the endothelium were mainly in the thin areas of the endothelial cells. Serial sections indicated that although some gaps were located at junctions between adjoining endothelial cells, most were through the endothelial plasma. Retraction of the endothelial cells may have provided the migration of tumor cells to the adjacent hepatocytes. The borders of the endothelial cells still connected by junctions remained intact for relatively long periods, which indicates that the extravasation was essentially transcellular. The endothelium on the luminal side of the invading cell was covered rapidly. After migration, the invading cells deeply invaded the adjacent hepatocytes, without becoming fully

intracellular. Small processes from the invaginating cells extended into the surrounding hepatocytes. These results are discussed in relation to the published data on WBC diapedesis and invasion and the available information on tumor cell invasion. (58 refs.)

78-1026 **Vascular Alterations in Focal Nodular Hyperplasia of the Liver.** (Eng) Travers, H. (Lab. Dept., Naval Regional Medical Center, Portsmouth, VA, 23708); D'Amato, N. A. *Milit Med* 143(2): 96-101; 1978.

Hepatic vascular alterations were studied in nine women and two men with focal nodular hyperplasia (FNH) of the liver and two women with hepatocellular adenoma. Both women with adenomas had used oral contraceptives, as had two women with FNH. In a few small arteries of FNH patients, an intimal proliferation of clear eosinophilic cells occluded the lumen of the vessels, but the internal elastic lamina appeared intact. This finding was noted regardless of history of oral contraceptive use. Variable intimal and medial hyperplasia with fragmentation of the elastic laminae occurred in both arteries and veins in cases of FNH; these changes were not present in adenoma cases. These data, as well as findings reported in the literature, suggest that FNH arises primarily from vascular injury to the liver. The lack of vascular injury in hepatic adenoma suggests that its pathogenesis is different from that of FNH and that the evolutionary relationship of the two lesions to oral contraceptives may involve different pathways. (15 refs)

78-1027 **Extrarenal Wilms' Tumor. Report of a Case and Review of the Literature.** (Eng) Akhtar, M. (Dept. Pathology, Univ. Texas Medical Sch. at Houston, Houston, TX); Kott, E.; Brooks, B. *Cancer* 40(6): 3087-3091; 1977.

A 2-mo-old boy developed a Wilms' tumor in the right groin. The tumor probably arose in the mesonephric nests, as it contained clusters of well-differentiated tubules and glomeruli. A review of the literature indicated that this is the 10th reported case of extrarenal Wilms' tumor. (9 refs.)

78-1028 **Hereditary Renal Cell Carcinoma: A New Syndrome Associated with a Chromosomal Translocation (Meeting Abstract).** (Eng) Cohen, A. J. (Dept. Medicine, Beth Israel Hosp., Boston, MA); Brown, R. S.; Berg, S. *Kidney Int* 12(6): 464; 1977. (no refs)

78-1029 **Suppression of Dysplasia and Hyperplasia by Calcium in Organ-cultured Urinary Bladder**



**Epithelium.** (Eng) Reese, D. H. (Lung Cancer Branch, NCI, NIH, Bethesda, MD, 20014); Friedman, R. D. *Cancer Res* 38(3): 586-592; 1978.

The development of endophytic growth (nodular down-growth) in rat urinary bladder epithelia cultured in protein-free medium was investigated. Endophytic growth, which is a characteristic in vivo histological feature of the preneoplastic phase of experimental bladder cancer, was induced in vitro by 0.3 mM  $\text{Ca}^{2+}$  but was suppressed by 1.8 mM  $\text{Ca}^{2+}$ . Magnesium at 1.8 mM had no effect on endophytic growth.  $\text{Ca}^{2+}$  concentrations above 0.9 mM resulted in a substantial inhibition of hyperplasia in the bladder epithelium; > 50% inhibition was observed with 1.8 mM  $\text{Ca}^{2+}$ . When the  $\text{Ca}^{2+}$  concentration was decreased to 0.075 mM and below, epithelial cells lost cohesiveness and infiltrated into the stroma. Epithelial cells were observed individually and in clusters within the lamina propria, indicating a breakdown in the basement membrane. Evidence of lytic activity was also observed in the lamina propria. Epithelial cells that infiltrated into the stroma displayed occasional mitotic figures and frequently contained abnormal nucleoli. The findings suggest that there may be an early change in some aspect of cellular  $\text{Ca}^{2+}$  (probably decreased binding) in epithelia and/or stroma that has been exposed to bladder carcinogens. In addition, the stimulation of infiltrative growth in calcium-deficient medium suggests that invading bladder cancer cells may have defects in control mechanisms that are normally regulated by  $\text{Ca}^{2+}$ . (22 refs)

**78-1030 Tumors in the Vesical Diverticula. Analysis of 17 Patients.** (Ger) Jacobi, G. H. (Urologische Klinik der Johannes-Gutenberg-Universität, Langenbeckstrasse 1, 6500 Mainz, W. Germany); Altwein, J. E. *Aktuel Urol* 8(5): 243-252; 1977.

During a 10-yr follow-up of 408 patients with bladder tumors, 17 (16 men) developed malignancies in the vesical diverticula. The main symptom of the second tumor was gross hematuria; bladder outlet obstruction occurred in 12 patients and significant urinary infection in 10. The period between onset of symptoms and diagnosis was approx 6 mo. There was a predominance of advanced growths and an increase in squamous cell carcinomas, compared to nondiverticula tumors. X-ray examination and cystoscopy were the best diagnostic tools. All patients underwent surgical treatment; the 5-yr survival was 29.4%, compared to 43% in the entire series. (38 refs.)

**78-1031 Seminoma in Two Nontwin Brothers.** (Fre) Perves, J. (Aix-en-Provence, France); Reboul, G. *J Urol Nephrol (Paris)* 83(10/11): 867-869; 1977.

The case histories of two brothers, aged 28 and 31, with a

seminoma are presented. Examination of other family members revealed no malignant tumors. Familial cases of testicular cancer are rare, but when they do occur, they are usually found in twins or in a father and son. Although these tumors are usually fatal within a few years, the brothers are well and 6 yr later, respectively. (3 refs.)

**78-1032 The Radiographic Demonstration of the Dynamic Transfer of Radio-Opaque Material from the Deferential Vein to the Prostate in the Dog.** (E) Dhabuwala, C. B. (Tenovus Inst. Cancer Res., Dept. Diagnostic Radiology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff, CF4XX, Wales, United Kingdom); Roberts, E. G. *Invest Urol* 15(4): 346-347; 1978.

Venous drainage of the canine prostate was studied in order to determine whether blood flow from the deferential vein could enter the intrinsic prostatic circulation directly. Five dogs were sedated, and radiopaque contrast medium injected into the deferential vein under firm hand pressure. In one dog, the contrast medium passed medially to enter into the cavernous venous plexus of the prostate urethra and the radiating veins of the prostatic parenchyma. The animal was not anesthetized deeply, and its irregular breathing probably contributed to passage of the medium into the prostatic vessels by intermittently increasing the venous pressure. In two dogs, constriction of the common iliac vein caused the contrast medium to pass from the prostaticovesical vein into the vein draining the cavernous plexus of the prostate urethra and from there to the plexus. Two dogs failed to show filling of the prostatic veins. No valves were detected in the prostatic vessels, and thus there is no natural resistance to this flow. Thus, there is a local system for transporting high androgen-containing blood from the deferential vein into the prostate. These findings reflect those of a previous study which showed that prostatic cancer spread to the spine by the retrograde flow of blood from the prostatic venous plexus to the extraprostatic vertebral veins. (6 refs)

**78-1033 Yolk Sac Carcinoma (Endodermal Sinus Tumor): Ultrastructure and Histogenesis of Caudal and Extragonadal Tumors in Comparison with Normal Human Yolk Sac.** (Eng) Nogales-Fernandez, F. (Dept. Pathology, Univ. Colorado Sch. Medicine, 4200 E. Ninth Ave., Denver, CO 80262); Silverberg, S. G.; Bloustein, P. A.; Martinez-Hernandez, A.; Pierce, G. B. *Cancer* 39(4): 1462-1477; 1977.

The ultrastructural features of three primary ovarian yolk sac carcinomas, omental metastases from one of these, and a primary retroperitoneal yolk sac carcinoma in a man were compared with those of the human yolk sac at 7 and 14 gestation. The most prominent feature of the tumors was the presence of voluminous basement membrane material



re of which was confirmed by the indirect enzyme-  
antibody technique in one case) in both intra- and  
cellular locations, corresponding to the PAS-positive  
globules seen in these tumors by light microscopy.  
Tumor cells also produced this material in tissue culture.  
ough basement membrane has not been found in the nor-  
human yolk sac at 8 and 10 wk gestation, it was present  
e 7-wk specimen, suggesting that its production may be  
ture of only the very young yolk sac. Other ultrastructur-  
findings were also similar in human yolk sac carcinoma,  
al human yolk sac, normal rodent yolk sac, and rodent  
sac carcinomas. Thus, these studies confirm the suggest-  
term cell-derived yolk sac origin of the human tumor. (38

034 **Bowen's Disease of Genital Areas. An Ultrastructural Study.** (Eng) Lupulescu, A. (Dept. Pathology, Wayne State Univ. Sch. Medicine, 323 Medical Building, 550 E. Canfield Ave., Detroit, MI 48201); Regan, A. H. *J Cutan Pathol* 4(5): 266-274; 1977.

Ultrastructural changes in specimens from five cases of Bowen's disease of genitalia are reported and compared with tissue from the surrounding normal skin. Electron microscopic findings included an advanced dyskeratosis, acantholysis due to dissolution of desmosomal-tonofilament complexes, enlarged nuclei and nucleoli, increased polysome populations, mitochondrial alterations, and nuclear inclusions similar to those seen in squamous cell carcinoma. The basement membrane remained intact and exhibited several deep infoldings protruding into the upper corium. Occasionally, atypical cells were undergoing cytolysis and were engulfed and phagocytosed by the neighboring keratinocytes (apoptosis). There were signs of increased DNA and protein synthesis in the basal epidermal cells. No papova virus-like bodies were found in the nuclei of anaplastic cells, but a few intracytoplasmic virus-like particles were present in several areas. The non-epithelium at the periphery of the lesion showed only a minimal degree of ultrastructural change. (10 refs.)

035 **Relationship Between HSV-2 Antigen and Colposcopic Findings.** (Ger) Gorcs, J. (Second Department of Gynecology, Baranya County Hospital, Sorház u. 4, 621 Pecs, Hungary); Kummerlander, L.; Pejtsik, B.; Pacz. *Arch Geschwulstforsch* 47(5): 437-439; 1977.

Colposcopic and cytological examinations were performed in 100 women using colposcopy and vaginal cytology. In addition, the cervical cells were examined for the presence of herpes simplex virus type 2 (HSV-2) antigen. Papanicolaou smears were found in 1,394 women, 14 of whom also had HSV-2 antigen. Papanicolaou III was found in 42 women, of whom were positive for HSV-2. Papanicolaou IV-V was found in four patients, in whom carcinoma in situ or mi-

crocarcinoma was diagnosed, and HSV-2 antigen was found in all four cases. The findings suggest a probable association of HSV-2 antigen with cervical cancer. (10 refs)

78-1036 **Squamous Metaplastic Cells in Cervical Canal Aspiration Smears in Women with Ovarian Function Disorders.** (Eng) Stanek, J. (ul. Krowoderskich Zuchow 24/82, PL-31-272 Krakow, Poland); Walas-Skolicka, E. *Arch Geschwulstforsch* 47(5): 440-443; 1977.

A comparison was made of the clinical findings and cytological data of 100 nonpregnant patients with ovarian function disorders and squamous metaplastic cells in their cervical aspiration smears (Group I) and 100 randomly selected patients with ovarian function disorders but without squamous metaplastic cells in their smears (Group II). Group I had less frequent hormonal therapy, more frequent cervical erosion, abnormal results of the water-salt test, and a diagnosis of hypothalamic postpregnancy syndrome. Vaginal smear patterns for Group I revealed a drift to the right in the maturation index; a higher superficial cell index, maturation value, and eosinophilic index; and a lower cytolytic index compared to Group II. No significant differences between the two groups with respect to crowded cell index, folded cell index, navicular cell index, urine excretion of 17-ketosteroids and 17-hydroxycorticoids, or morphology of cervical mucus were observed. It is suggested that disturbances in the neurohormonal backgrounds of the Group I women are important in the pathogenesis of endocervical metaplasia and that this metaplasia may play a role in carcinogenesis. (17 refs)

78-1037 **Ultrastructure of the Benign and Borderline Brenner Tumours.** (Eng) Klemi, P. J. (Dept. Pathological Anatomy, Univ. Turku, Kiinamyllynkatu 10, 20520 Turku 52, Finland); Nevalainen, T. J. *Acta Pathol Microbiol Scand [A]* 85(6): 826-838; 1977.

Two ovarian Brenner tumors, one benign and one of borderline malignancy, were studied by electron microscopy. Ultrastructurally, the cells of both tumors were similar. The intercellular spaces were large and reinforced by a moderate number of desmosomes. The nuclei were round or oval; the nuclear membrane was irregular in shape, with deep infoldings corresponding to the characteristic nuclear groovings seen by light microscopy. The benign tumor contained few secreting cells. However, the cystic cavities of the borderline tumor were lined by nonciliated secreting and ciliated nonsecreting cells. The secretory granules were PAS-positive and diastase-resistant. They stained homogeneously and strongly with PAS methenamine, indicating the presence of 1,2-hydroxyl groups. The Brenner tumors have many characteristics of transitional epithelium and of müllerian-derived tubular structures. The findings support the concept that these tumors are of celomic origin and develop by direct metaplasia from the ovarian surface epithelium. (46 refs)



- 78-1038 Carcinoma of the Endometrium: Radiation Followed Immediately by Operation.** (Eng) Underwood, P. B. (Dept. Obstetrics and Gynecology, Medical Univ. South Carolina, 80 Barre St., Charleston, SC 29401); Lutz, M. H.; Kreutner, A.; Miller, M. C.; Johnson, R. D. *Am J Obstet Gynecol* 128(1): 86-98; 1977.

A prospective study was established in August 1967 to treat all endometrial adenocarcinomas by preoperative radiation followed immediately by surgery. Of the 295 women treated, 220 had Stage I adenocarcinomas for which the primary mode of therapy was preoperative radium followed by total hysterectomy and bilateral salpingo-oophorectomy. Life tables demonstrated a 5-yr survival rate of 91% and a low complication rate in patients with Stage I disease. Cell type, degree of differentiation, and depth of endometrial invasion were the primary factors influencing survival. Only one recurrence occurred among the 44 premenopausal women and the 62 who had received exogenous estrogens. Thus, estrogen-associated endometrial adenocarcinoma may be a less aggressive disease. (18 refs.)

- 78-1039 Hyperplastic States of the Endometrium and Their Correlations with Endometrial Carcinoma.** (Ger) Ritzman, H. (Universitäts-Frauenklinik, D-7800 Freiburg im Breisgau, W. Germany); Hillemanns, H. G. *Arch Gynaekol* 223(4): 345-355; 1977.

The incidence of adenomatous hyperplasia (AH) and glandular-cystic hyperplasia (GCH) of the marginal endometrium was surveyed in 196 patients hysterectomized for carcinoma of the uterus and in 208 patients hysterectomized for nonneoplastic conditions (controls). The average age of all carcinoma patients was 61.9 yr, that of patients with carcinoma and AH 52.2 yr, and that of patients with carcinoma and GCH 60.8 yr. The incidence of AH and GCH in the carcinoma patients was 19.3% and 17.8%, respectively. In the age bracket 45-49 yr, the incidence of AH was 31.5% in the carcinoma patients vs 4.5% in controls. The incidence of GCH was 10.5% vs 6.1% in controls, the difference not being significant. In the age bracket 50-54 yr, the incidence of AH and GCH was 26.4% and 11.7% in the carcinoma patients and 1.6% and 4.9%, respectively, in controls. The difference for GCH is not significant. In the age bracket 55-59 yr, the incidence of AH and GCH was 25% and 15.9%, respectively, in the carcinoma patients and 0% and 0% in controls. In the age bracket 60-65 yr, the incidence of AH and GCH was 13.4% and 25%, respectively, vs 0% and 16.1% in controls. Above the age of 65 yr, the incidence of GCH was 20.5% in the carcinoma patients and 3.8% in controls, but there was no significant difference for GCH (7.7% vs 9.8% in controls). The simultaneous occurrence of AH and endometrial carcinoma suggests that this form of hyperplasia is precancerous. Before menopause, GCH does not seem to play any essential etiological role in the genesis of endometrial cancer. The cause of the increased incidence of GCH in postmenopausal women with endometrial carcinoma is not

known. Estrogens may form a good substrate for endometrial cancer. (36 refs.)

- 78-1040 Clear Cell Adenocarcinoma of the Uterus: Ultrastructural and Hormonal Study.** (Eng) Nishimura, A. (Div. Pathology, Kyushu Cancer Center, 585 Nishiku, Minamiku, Fukuoka 815, Japan); Yasumoto, K.; Ueda, W.; Watanabe, Y.; Kotoo, Y.; Kurita, Y. *Acta Pathol Jpn* 27(5): 907-915; 1977.

An ultrastructural and hormonal study was made of a clear cell adenocarcinoma of the uterus plus early invasive squamous cell carcinoma of the cervix in a 47-yr-old woman. The epithelial cells of the adenocarcinoma contained junctional complexes, well-developed microvilli, parallel stacks of granular endoplasmic reticulum, and twisted ropelike cilia, characteristics similar to those of endometrial carcinoma. Analysis of a pulmonary metastasis showed high estradiol levels in the tumor tissue and high estrone and estradiol levels in a cell suspension. The filtrate of a tumor culture showed high levels of human chorionic gonadotropin. Comparison of the estrogen effect in vaginal smears taken before and after hysterosalpingo-oophorectomy indicated that blood estrogen was lower after treatment. These findings support the view of a müllerian duct origin of uterine clear cell adenocarcinoma. (17 refs)

- 78-1041 Ultrastructural Observations on Benzo(a)pyrene-induced Squamous Cell Metaplasia in the Decidual Endometrium of the Rat Uterus.** (Meeting Abstract). (Eng) Kang, Y. H. (Dept. Pharmacology, Howard Univ. Cancer Center, Washington, D.C., 20059); Lin, T. H.; West, W. L.; Sperling, F. *Proc Am Assoc Cancer Res* 19: 190; 1978. (no refs)

- 78-1042 Extramammary Paget's Disease of the Vulva: A Histogenetic Study (Meeting Abstract).** (Eng) Roth, L. M. (Indiana Univ. Sch. Medicine, Indianapolis 46202); Lee, S. C.; Ehrlich, C. *Am J Clin Pathol* 69(2): 1978. (no refs)

- 78-1043 Oestrogen Receptors in Transplantable Ovarian-independent, Mammary Tumours of the Rat.** (Eng) Hawkins, R. A. (Dept. Clinical Surgery, Univ. Edinburgh, Edinburgh, Scotland); Hill, A.; Freedman, B.; Kohn, E.; Miller, W. R. *Eur J Cancer* 14(1): 83-90; 1978.

Estrogen receptor levels (ERL) were measured in the tumor and in the plasma of rats bearing transplantable 7,12-dimethylbenz(a)anthracene (DMBA)-induced



mmary carcinomas TG3, TG5, and TG6 implanted sc in age-Dawley rats. Tumors induced by DMBA (30 mg illed intragastrically) in random-bred rats were used for parison. Low estrogen receptor activity was noted in all 3 and TG5 tumors; receptor activity was found in only TG6 tumors, and it was extremely low. Ovariectomy of nals with TG3 or TG5 tumors had no significant effect ERL, but prolactin levels were significantly reduced. rteen days after ovariectomy, ERL were significantly her in the DMBA-induced tumors, which regressed, n in the nonregressed TG3 or TG5 tumors. When rietomized animals were treated with estrogen, L in the ovary-dependent DMBA-induced tumors e higher ( $p < 0.01$ ) than those in the ovary- dependent, transplantable tumors. Furthermore, L in the uncharacterized DMBA-induced tumors e significantly higher than ERL in the transplant- umors. However, the overlap between the values for the ced and transplanted tumors suggests that there is no r division between ovary-dependent and ovary- dependent tumors. (25 refs.)

1044 **Comparative Ultrastructural and Cytochemical Studies of Rat Lactating Mammary Gland and 7,12-Dimethylbenz(a)anthracene-induced Mammary Tu- (Meeting Abstract).** (Eng) Zemichael, D. (Dept. Zoolo-Howard Univ. Cancer Center, Washington, D.C., 20059). *Am Assoc Cancer Res* 19: 190; 1978. (no refs)

1045 **Elevated Serum NMR Relaxation Times at the Preneoplastic to Neoplastic Transformation in Mammmary Cancer (Meeting Abstract).** (Eng) Beall, . (Baylor Coll. Medicine, Houston, TX, 77030); Medina, Hazlewood, C. F. *Fed Proc* 37(3): 232; 1978. (no refs)

1046 **Parallel Changes of the Epithelium and Stroma in Recurrent Fibroadenoma of the Breast.** (Pol) szko, P. (Instytut Patologii, ul. Grzegorzeczka 16, 31-531 ow, Poland); Kostyrka, J. *Patol Pol* 28(4): 469-475; 1978.

case report of a 24-yr-old woman with recurrent fi- denoma of the breast is presented. The predominant phological features of the tumor were simultaneous dys- ia and atypia of both the glandular cells and stroma. The istence of a gynecological illness (ovarian teratoma and strual disorders) in this patient may have been a factor e recurrent disease. (22 refs)

78-1047 **Angiogenesis as a Marker of Preneoplastic Le- sions of the Human Breast.** (Eng) Brem, S. S. (Dept. Neurosurgery, Massachusetts General Hosp., Boston, MA, 02114); Jensen, H. M.; Gullino, P. M. *Cancer* 41(1): 239-244; 1978.

At the time of biopsy or mastectomy, 947 tissue fragments from 42 patients were transplanted onto rabbit irises to deter- mine their ability to induce new vessel formation. At least one transplanted fragment from 10/10 carcinomas induced a strong angiogenic response. Of 50 transplants from hyper- plastic lobules, 28% also induced angiogenesis. Fibrous or adipose tissue and tissues from normal lobules, fibrocystic disease, fibroadenoma, lipoma, and gynecomastia rarely pro- duced angiogenesis. In the mouse, the frequency of neoplastic transformation is higher in hyperplastic lesions with a high frequency of angiogenic response. Thus, it should be deter- mined whether breast carcinoma frequency is higher in hu- man subjects whose hyperplastic lesions elicit a strong angio- genic response. The angiogenic assay could distinguish lesions undergoing malignant transformation before mor- phologic signs of atypia and invasion appear. (26 refs)

78-1048 **Electron Microscopic Study on Vascular Inva- sion of Choriocarcinoma Heterotransplanted on Nude Mouse.** (Eng) Kawagoe, K. (Dept. Obstetrics and Gynecology, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan); Sugase, M.; Kawana, T.; Sakamoto, S. *Nippon Rinsho Denshi Kenbikyo* 10(3/4): 265-272; 1977.

A human choriocarcinoma was transplanted to the back of a nude mouse, and the invasion of host vessels by tumor cells was studied electron microscopically. Morphological changes of the vessels were observed in relation to the distance be- tween the tumor cell and the endothelial cell. Tumor cells at the invading site had short, thick microvilli and cytoplasmic protrusions on their surfaces. Desmosomes were observed between the tumor and endothelial cells. The role of opened endothelial cell junctions in the penetration of the vascular lumina by tumor cells is evaluated. (10 refs)

78-1049 **Phalangeal Metastases from Bronchogenic Car- cinoma.** (Eng) Vaezy, A. (Dept. Medicine, Div. Pulmonary Diseases, Univ. North Carolina, Chapel Hill, NC 27514); Budson, D. C. *JAMA* 239(3): 226-227; 1978.

Two men, aged 52 and 48 yr, each had squamous cell car- cinoma of the lung and unusual phalangeal metastases. The former presented with a swollen middle phalanx of the right fourth finger; subsequent studies showed metastases there and in the right fifth finger and both great toes. The latter



presented with symptoms of gout; metastases were detected in right great toe and right third finger. (3 refs.)

- 78-1050 Enhancement of Experimental Lung Metastases by Melanoma Cells Treated with ICRF-159 (Meeting Abstract).** (Eng) Lazo, J. S. (Yale Univ. Sch. Medicine, New Haven, CT, 06510); Ingber, D. E.; Sartorelli, A. C. *Fed Proc* 37(3): 316; 1978. (no refs)

- 78-1051 Cascade Spread of Blood-Borne Metastases in Solid and Non-Solid Cancers of Man (Meeting Abstract).** (Eng) Viadana, E. (Shadyside Hosp., Pittsburgh, PA, 15232); Bross, I. D.; Pickren, J. W. *Proc Am Assoc Cancer Res* 19: 2; 1978. (no refs)

- 78-1052 Anti-Metastatic Factor(s) in Normal Plasma (Meeting Abstract).** (Eng) Vaage, J. (Dept. Cancer Therapy Development, Pondville Hosp., Walpole, MA, 02081). *Proc Am Assoc Cancer Res* 19: 1; 1978. (no refs)

- 78-1053 Endometrial Carcinoma and Amyloidosis after Kidney Transplantation.** (Eng) Thoua, Y. (Brugmann Hosp., Brussels Univs., Brussels, Belgium); Dupont, E.; Kinnaert, P.; Vereerstraeten, P.; Potvliege, P.; Van Geertruyden, J.; Toussaint, C. *Transplantation* 25(2): 91-92; 1978.

A 41-yr-old woman developed endometrial adenocarcinoma 4 yr after receiving a kidney transplant. She had been treated with immunosuppressive therapy during six rejection crises in the intervening 4 yr. Postmortem 5 yr after transplantation revealed amyloid deposits in the spleen, myocardium, and transplant. The recipient of the donor's other kidney is free of amyloid deposits 7 yr postoperatively. The carcinoma and amyloidosis could have been induced by antigenic stimulation or immunosuppressive therapy. (13 refs)

- 78-1054 Squamous Cell Carcinoma of the Tongue in a Nine Year Renal Transplant Survivor. A Case Report with a Discussion of the Risk of Development of Epithelial Carcinomas in Renal Transplant Survivors.** (Eng) Lee, Y. W. (Dept. Pathology, Northern Div., Albert Einstein Medical Center, York and Tabor Roads, Philadelphia, PA, 19141); Gisser, S. D. *Cancer* 41(1): 1-6; 1978.

A 26-yr-old man developed a squamous cell carcinoma of the tongue 9 yr after receiving a renal transplant. Within 7 mo,

widespread tumor metastases resulted in death. Pathologic examination of the transplanted kidney revealed no evidence of rejection or recurrent glomerulonephritis, and lack of significant renal disease was confirmed by electron microscopy. The tongue neoplasm developed in the absence of tobacco use or chronic irritation, indicating that renal transplantation and immunosuppression were the contributory factors. The number of long-term renal transplant survivors increases; there may be an increased incidence of nonlymphomatous neoplasms in these patients. (13 refs)

- 78-1055 Chronic Granulocytic Leukemia in a Renal Transplant Recipient.** (Eng) Mooy, J. M. (Urology Hosp., Rotterdam-Dijkzigt, Netherlands); Hagenouw-Timmer, J. C.; Lameijer, L. D.; van Turnhout, J. M. *Cancer* 41(1): 1; 1978.

A 44-yr-old man developed Philadelphia chromosome positive chronic granulocytic leukemia 4 yr after a kidney transplant. He had received 150 mg azathioprine and 15 mg prednisone daily for 2 yr before development of the leukemia. Since the former is known to induce chromosomal abnormalities in lymphocyte cultures and bone marrow cells, a direct oncogenic action cannot be ruled out. (25 refs)

- 78-1056 Acute Myeloblastic Leukemia 8 Yr after Kidney Transplant (Letter to Editor).** (Fre) Ueda, Y. (Centre d'Anatomie Pathologique, Hopital Universitaire de Tokyo Hongo, Tokyo 113, Japan); Taguchi, T.; Shimizu, T.; Takayasu, T. *Nouv Presse Med* 7(5): 371; 1978.

Acute myeloblastic leukemia occurred in a 40-yr-old man 8 yr after he received a kidney transplant from his brother. The immunological tests showed histocompatibility except for the mixed lymphocyte culture test. There was no evidence of rejection during immunodepressant treatment (prednisone, 10 mg/day, and imuran, 75 mg/day) until 2 yr after the transplant surgery. Renal function gradually deteriorated from April 1970 until the patient's death from pneumonia in September 1975. Just 1 mo prior to death, the patient's blood showed myeloblastemia and thrombocytopenia. Autopsy examination of kidney showed histological evidence of chronic rejection. In the bone marrow, there were myeloblastic infiltrations intermingled with megakaryocytes. Leukemic infiltration was observed in the spleen, lymph nodes, kidney, liver, and lungs. Malignant hemopathies following renal transplants are not as frequent as lymphomas and skin and cervical carcinomas. (3 refs)

- 78-1057 Myogenic Cells in Kaposi's Sarcoma: An Ultrastructural Study.** (Eng) Harrison, A. (Dept. Pathology, Univ. Cape Town Medical Sch., Cape Town, South Africa).



yn, South Africa); Kahn, L. B. *J Pathol* 124(3): 157-160; 1978.

ultrastructural study of a metastatic Kaposi's sarcoma in cervical lymph node demonstrated the presence of endothelial cells, smooth muscle cells, fibroblasts, and myofibroblasts. Some of these cells exhibited phagocytic activity in relation to extravasated RBC. These observations favor the hypothesis that this tumor originates from a pluripotential mesenchymal cell that can differentiate into the more specialized connective tissue cell types observed in the tumor. (12 refs)

058 **A Study of Malignant Lymphomas Using Light and Ultramicroscopic, Cytochemical and Immunologic Technics. Correlation with Clinical Features.** (Eng) Filippa, D. A. (Dept. Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021); Lieberman, P. H.; Erlandson, R. A.; Koziner, B.; Hsu, F. P.; Turnbull, A.; Zimring, A.; Good, R. A. *Am J Pathol* 104(2): 259-268; 1978.

light microscopic and ultrastructural morphology, enzyme cytochemistry, and cell-surface and functional markers of lymphoreticular tissue were determined in 50 patients (27 men, 23 women aged 15-79 yr) with non-Hodgkin's lymphoma. In 40 patients, a predominant population of monoclonal B cells was found. One cell type within this group could be recognized by a faint surface membrane immunofluorescence; this type appeared identical to the cells in chronic lymphocytic leukemia. A second cell type was characterized by its bright surface immunoglobulin; two subtypes were recognizable by light and electron microscopy. The other cell type characterized by its ability to phagocytize, positive staining for nonspecific esterases, and its dense cytoplasmic granules was found in one patient with acute myelocytic leukemia. A fourth cell type was identified in two patients; these cells formed rosettes with sheep RBC at 4°C, indicating a T-cell lineage. A fifth cell type with no cell markers was noted in two acute leukemia patients. In five patients, no identifiable clonal proliferation could be established. These findings suggest the usefulness of cell markers for the identification of cellular types, providing more objectives for the prognosis and treatment of lymphoreticular diseases. (60 refs)

059 **Malignant Lymphoma and Extensive Viral Wart Formation in a Patient with Intestinal Lymphangiectasia and Lymphocyte Depletion.** (Eng) Ward, J. (Gastro-intestinal Unit, Western General Hosp., Edinburgh, Scotland); Small, W. P.; Le Roux, A.; Sircus, W. *Postgrad Med J* 53(626): 753-757; 1977.

case report of a 40-yr-old man with malignant small

bowel lymphoma is presented. Extensive viral warts had been present since the age of 18, and marked lymphocyte depletion had been diagnosed at age 29. Local resection of the tumor and radiotherapy treatment were applied, but the patient died soon after surgery. Despite the downhill course, the warts had almost completely disappeared from his hands; the reason for this is uncertain. Chronic antigenic stimulation by the virus could have played a role in the development of malignancy, or the lymphocyte depletion may have led to both the warts and malignancy. (12 refs)

78-1060 **Primary Intracranial Malignant Lymphomas with Particular Reference to Their Pathogenesis.** (Eng) Tanaka, T. (Pathology Section, Central Labs., Okayama Univ. Medical Sch., Okayama 700, Japan); Nishimoto, A.; Doi, A.; Nagao, S.; Hujita, M.; Sezaki, T.; Yumoto, T. *Acta Pathol Jpn* 27(6): 927-940; 1977.

Six cases of primary intracranial malignant lymphoma (in 4 men, 2 women aged 42-68 yr) diagnosed between 1966 and 1971 are discussed. These cases amounted to 1.9% of all primary brain tumors encountered during this period. The tumors were located in the frontal, temporal, parietal, or occipital lobes or deep in the thalamus, and they weighed 15-150 g. The most reliable diagnostic feature was a perivascular cuffing with tumor spread into the surrounding tissue. Two cases had numerous histiocytes with foamy cytoplasm intermingled with the tumor cells. Because of their histologic similarity to extracerebral malignant lymphomas, these tumors should be regarded as primary malignant lymphomas of the CNS and not as reticulum cell sarcomas-microgliomas. Injury to the multipotent, fixed, mesenchymal brain cells may cause them to proliferate and form tumors. (21 refs)

78-1061 **Comparative Morphologic and Morphometric Study on the Perichromatin Granules in Normal and Tumour Lymph Node Cells.** (Eng) Vulkov, I. N. (Dept. Anatomical Pathology, Medical Acad., Sofia, Bulgaria); Vassilev, N. B. *Dokl Bolg Akad Nauk* 30(9): 1347-1350; 1977.

The morphology of the perichromatin granules (PCG) in lymph nodes from patients with various benign or malignant diseases was evaluated. There were 8 patients with lymphadenitis, 6 with Hodgkin's disease, 3 with lymphoblastic lymphoma, and 2 with metastatic adenocarcinoma. PCG were found throughout the nucleus near the dense chromatin borders. They were always surrounded by a clear halo that was occasionally interrupted by chromatin fibers. In normal lymphocytes, the PCG were round or slightly oval. In certain nonmalignant cells (from viral lymphadenitis), the PCG were pleomorphic. In the cancer cells, they were very pleomorphic, with elongated to dumbbell-like shapes. Some PCG had electron-dense rays, and they appeared as stellate figures. The irregular ribonuclear protein fibers in these cells were not



bleached by EDTA, and the cells had an asymmetric halo. The PCG in the nuclei had diameters exceeding those of normal lymphocytes and lymphoblasts. The PCG tended to be most elongated in the Hodgkin's disease and Sternberg cells. (11 refs)

- 78-1062 Familial Myeloperoxidase Deficiency and Acute Myelogenous Leukemia.** (Ger) Huhn, D. (Medizinische Klinik III, Klinikum Grosshadern der Universität München, Marchioninistrasse, D-8000 Munich 70, W. Germany); Belohradsky, B. H.; Haas, R. *Acta Haematol (Basel)* 59(3): 129-143; 1978.

A 15-yr-old boy suffering from acute myelogenous leukemia was found to be lacking myeloperoxidase (MPO) during the acute phase of the disease and during partial hematological remission. Ultrastructurally, the neutrophils and monocytes appeared normal, but no MPO activity could be demonstrated. A partial MPO deficiency was found in the patient's father, but no abnormalities were found in other relatives. Less than 50% of the neutrophils had a normal MPO concentration in the father; the other neutrophils and most monocytes were MPO-negative. Neutrophil bactericidal activity was strongly inhibited in the patient and decreased in his father. Normal values were found in the blue tetrazolium test, chemotactic function, serum-dependent phagocytosis, B- and T- lymphocyte counts, serum immunoglobulins, and complement in both the patient and his father. Partial MPO deficiency is not uncommon in leukemia patients; 8%-70% of the neutrophils were MPO-negative in 12/28 patients with acute myelogenous leukemia in one series. In rare cases, varying percentages of MPO-negative neutrophils are found in patients with refractory anemia. In these patients the enzyme defect is suggestive of the existence of preleukemia. The findings and the literature data suggest a possible relationship between MPO deficiency and leukemia. (33 refs)

- 78-1063 Elevated Sister Chromatid Exchange Rate in Childhood Acute Lymphoblastic Leukemia (Meeting Abstract).** (Eng) Otter, M. (Indiana Univ. Sch. Medicine, Indianapolis, IN, 46202); Palmer, C. G.; Baehner, R. L. *Proc Am Assoc Cancer Res* 19: 202; 1978. (no refs)

- 78-1064 Frequency of Chromosome 1 qh+ in Chronic Myeloid Leukemia.** (Fre) Berger, R. (Institut de recherches sur les leucémies et les maladies du sang, Hôpital Saint-Louis, 2, place du Docteur-Fournier, 75475 Paris Cedex 10, France); Bernheim, A. *C R Acad Sci [D] (Paris)* 285(12): 1183-1185; 1977.

Bone marrow and cultured blood cells (with or without phytohemagglutinin) from 83 subjects were analyzed for

chromosomal anomalies. The C band of chromosomes 1 and 16 was classified according to length as N, +, or -; incidence of chromosome 1 qh+ was significantly higher ( $< 0.05$ ) in chronic myeloid leukemia (CML) patients (20/20) than in controls (8/17) and patients with other hematological disorders, including acute leukemia (7/14), myeloproliferative syndromes (4/9), polycythemia vera (3/8), medullary aplasia (1/6), and Fanconi's anemia (2/5). The frequency of C-band variants of chromosomes 9 and 16 did not differ significantly in CML patients compared to normal subjects or patients with other blood disorders. The presence of chromosome 1 qh+ is not a consequence of CML, since it was observed on normal lymphocytes as well as on those with characteristic Philadelphia chromosome. (4 refs.)

- 78-1065 Duplication of Part of Chromosome No. 1 in Myeloproliferative Diseases (Letter to Editor).** (Eng) Gahrton, G. (Section Oncology and Hematology, Dept. Medicine, Huddinge Univ. Hosp., S-141 86 Huddinge, Sweden); Friberg, K.; Zech, L.; Lindsten, J. *Lancet* 1(8096-97): 1978.

Of seven patients with polycythemia vera or myelofibrosis terminating in acute myeloblastic leukemia, all had a duplication of the q23-25 region on chromosome 1. This duplication may be crucial in the development of certain myeloproliferative diseases. (9 refs.)

- 78-1066 Chromosomes and Causation of Human Carcinoma and Leukemia. XXX. Banding Studies of Primary Intestinal Tumors.** (Eng) Sonta, S. (Roswell Park Memorial Inst., 333 Elm St., Buffalo, NY, 14263); Sandberg, A. A. *Cancer* 41(1): 164-173; 1978.

The chromosomes of 15 primary intestinal tumors were analyzed by a Q-banding technique. Of the 15 tumors, 8 had changes in chromosome number and 4 had both numerical and structural chromosome abnormalities. The remaining three tumors showed no karyotypic abnormalities. No common marker chromosomes were seen among the various tumors, and no two tumors with chromosome changes had identical karyotypes. Chromosomes 8, 13, 15, 17, and 21 were participated as extra chromosomes in 7, 4, 4, 6, and 6 tumors respectively. Chromosome losses, although much less frequent, involved chromosomes 5, 6, 7, 10, and 16. Most tumor cells with chromosome changes were hyperdiploid, and usually contained  $< 60$  chromosomes. Only one tumor, colon carcinoma, contained hypodiploid cells. Although some chromosomes were not missing, as has been observed in leukemia, some of the extra chromosomes observed in this series are also involved as extra chromosomes in chronic myeloid leukemia and acute myeloblastic leukemia. (17 refs)



**1067 Chromosomal Alterations in Human Carcinogenesis.** (Ita) Feo, F. (No affiliation given). *Nerv Med* 69(3): 216-219; 1978.

cytotypic changes in hereditary diseases associated with tumors, the aneuploidy of human tumor cells, and the presence of abnormal chromosomes in tumor cells are indicative of a relationship between chromosomal aberrations and carcinogenesis. Changes in the karyotype may contribute to tumor progression. (no refs.)

**1068 Chromosome Instability and Malignant Growth.** (Rus) Bochkov, N. P. (Inst. Medical Genetics, Moscow, USSR); Kuleshov, N. P. *Vestn Akad Med Nauk SSSR* (10): 54-59; 1977.

The frequency of spontaneous chromosome aberrations was studied in 23 patients with ataxia-telangiectasia. The karyotypes showed a high frequency of metaphases: broken chromosomes and rearrangement (8.4%, vs 1.0% in controls), endoreduplication (4.5% vs 0.3%), and polyploidy (1.0% vs 0.6%). Chromosome rearrangement primarily involved chromosome 14. The abnormal chromosomes from all patients showed stable proliferation in culture. The cell lines from 3 patients had karyotype 46,t(Dq/Cq+), 2 had karyotype 46,t(Dq-Dq+), 1 had 46,Dq-, 1 had 47,+C, and 1 had 46,t(Dq-Dq+)/47+C. (16 refs.)

**1069 Transfer of the Marker for Morphologically Transformed Phenotype by Isolated Metaphase Chromosomes in Hamster Cells.** (Eng) Spandios, D. A. (Dept. Medical Genetics, Univ. Toronto, Toronto, Ontario, Canada M5S 1A8); Siminovitch, L. *Nature* 271(5642): 259-261; 1978.

The ability of purified metaphase chromosomes from Chinese hamster ovary (CHO) cells to transfer the marker for a morphologically transformed phenotype was examined. Purified metaphase chromosomes were added to cloned senescent cultures that were then incubated for 3 wk, after which colonies were counted and isolated. Colonies were obtained in 5/6 cultures treated with metaphase chromosomes, whereas no colonies were obtained when the senescent cells were plated without previous addition of the chromosomes. No colonies were obtained when metaphase chromosomes were added to plates in the absence of recipient cells. Morphologically, rescued senescent cells had the appearance of transformed cells, and this transformed phenotype was maintained on continued culture of these clones. Metaphase chromosomes from CHO cells were fractionated into three class sizes in sucrose gradients, and each fraction was tested for its ability to rescue senescent recipient hamster cells. Activity was found in the large-size class of chromosomes, but few or no colonies were obtained with the other fractions. Thus, the

ability to transform cells is located on a specific size class of chromosomes and it behaves similarly to other genetic markers. It is concluded that the addition of CHO metaphase chromosomes to senescent cells provides genetic information resulting in the transformation phenotype; the frequency of this event is similar to that of single gene markers. (11 refs.)

**78-1070 Agnogenic Myeloid Metaplasia: A Clonal Proliferation of Hematopoietic Stem Cells with Secondary Myelofibrosis.** (Eng) Jacobson, R. J. (Div. Hematology-Oncology, Dept. Medicine, Univ. Witwatersrand, Johannesburg, South Africa); Salo, A.; Fialkow, P. J. *Blood* 51(2): 189-194; 1978.

The glucose-6-phosphate dehydrogenase (G-6-PD) types and chromosomes of hematopoietic and other tissues were determined in a 70-yr-old woman with agnogenic myeloid metaplasia. The patient was heterozygous at the X-linked G-6-PD locus, so her nonhematopoietic cells contained approx equal amounts of the B and A isoenzymes. In contrast, only the A enzyme was detected in granulocytes, RBC, and platelets. A distinctive chromosome abnormality (47,XX,+8) was present in blood cells but not in other tissues. These results indicate that agnogenic myeloid metaplasia is a disorder of a pluripotent stem cell and is of clonal origin. The marrow fibrosis associated with the disease is probably a secondary abnormality, since this patient's cultured marrow fibroblasts had normal chromosomes and the B and A G-6-PD isoenzymes. If agnogenic myeloid metaplasia is of clonal origin, by inference, the disease should be neoplastic. (19 refs)

**78-1071 Insulin-Containing RBC Carcinogenesis.** (Ukr) Chumak, D. A. (Medical Inst., Chernovtsy, USSR); Sandulyak, L. I.; Baeva, O. V.; Andrusenko, V. A. *Dopov Akad Nauk Ukr RSR [Ser B]* (10): 946-948; 1977.

To evaluate a possible role of insulin in tumorigenesis, the number of insulin-containing RBC was assessed in 17 patients with Stages II-III breast carcinoma, 34 patients with Stages II-IV cancer of the stomach, and 25 practically healthy subjects. The fasting glucose level in healthy controls was 95 mg%, compared to 68 mg% in the patients with breast carcinoma, and 70 mg% in patients with cancer of the stomach. The cytochemical assay detected 70% of the insulin-containing RBC in the healthy controls, 54% of those in stomach cancer patients, and 35% of those in breast cancer patients. (10 refs)

**78-1072 Topography of Nonneoplastic and Neoplastic Cells of Common Origin.** (Eng) Wetzel, B. (Der-



matology Branch, NCI, NIH, Bethesda, MD 20014); Sanford, K. K.; Fox, C. H.; Jones, G. M.; Westbrook, E. W.; Tarone, R. E. *Cancer Res* 37(3): 831-842; 1977.

The topography of neoplastic and nonneoplastic cells from a 12-day C3Hf/HeN mouse embryo was examined by scanning electron microscopy. The cells were assayed for neoplastic activity by injecting them into x-irradiated syngeneic hosts; all tumors that developed were sarcomas. A total of 19 cultures from 6 nonneoplastic lines and 26 cultures from 9 neoplastic lines were examined. Eighty-five percent of the neoplastic lines lacked microvilli compared to 79% of the nonneoplastic cells. Film analyses indicated that the incidence of ruffles and blebs did not correlate with the neoplastic state. Most neoplastic lines showed less flattening or spreading on the coverslip than nonneoplastic cells, and the neoplastic lines also contained more cells with abundant lateral processes. There was no pattern of morphological change as a function of postmitotic time in either group. Cells with exaggerated surface features, although present in neoplastic cultures, cannot be taken as examples of all transformed cells. (42 refs.)

**78-1073 Morphometric Analysis of Neoplastic Transformation in Rodent Fibroblast Cell Lines.** (Eng)

Fox, C. H. (Lab. Biochemistry, Cell Physiology and Oncogenesis Section, NCI, Building 37, 4D-07, NIH, Bethesda, MD 20014); Caspersson, T.; Kudynowski, J.; Sanford, K. K.; Tarone, R. E. *Cancer Res* 37(3): 892-897; 1977.

Morphologic changes accompanying neoplastic transformation were studied in normal and transformed cell lines of

common origin from 18-day Fischer rat embryos, 11-ALB/N rat embryos, 13-day C3Hf/HeN embryos, 13-C3H/HeN embryos, or a clone from 13-day C3Hf/HeN embryos. Neoplastic transformation was accompanied by crease in the projected area of the lamellar cytoplasm, a crease in the projected area of the nucleus, and a decrease in the dry mass of the lamellar cytoplasm. UV absorption 265 nanometers was generally less in the neoplastic cells than in the nonneoplastic cells; nuclear mass remained approximately the same. These findings indicate that neoplastic transformation is not only accompanied by changes in the cellular membranes, but also by cytoplasmic changes. (20 refs.)

*See also:*

\*(Rev.): 78-0649, 78-0655, 78-0658, 78-0659, 78-0661, 78-0662, 78-0663, 78-0666, 78-0669, 78-0671, 78-0672.

\*(Chem.): 78-0678, 78-0685, 78-0687, 78-0695, 78-0701, 78-0709, 78-0718, 78-0727, 78-0728, 78-0744, 78-0748, 78-0755, 78-0769, 78-0782, 78-0783, 78-0793, 78-0802, 78-0803, 78-0808.

\*(Phys.): 78-0813, 78-0815, 78-0816, 78-0818, 78-0821, 78-0828.

\*(Viral): 78-0844, 78-0861, 78-0896, 78-0913, 78-0918.

\*(Immun.): 78-0945, 78-0951, 78-0959, 78-0968, 78-0981, 78-0988, 78-0991.

\*(Epid.-Biom.): 78-1079, 78-1085, 78-1087, 78-1101, 78-1102, 78-1103, 78-1108, 78-1109, 78-1110, 78-1141, 78-1143.



## EPIDEMIOLOGY AND BIOMETRY

- 1074 **Errors in Reporting Cancer and Other Conditions by Persons in a Prospective Study.** (Eng) Ono, J. (Japan-Hawaii Cancer Study, 347 N. Kuakini St., Kuakini Medical Center, Honolulu, Hawaii, 96817); Nomura, A. *Public Health Rep* 93(1): 11-15; 1978.

An attempt was made to verify the accuracy of medical histories obtained by interview by a systematic review of the past hospital records of 553 men with cancer and other diseases. For the 61 cancer patients, the average interval from the date of diagnosis to the date of interview was 2.3 yr, with a range of 2 mo to 17 yr. Forty of the cancer patients stated that they had the condition. However, 21 cancer patients did not give a positive history of their disease, and 4 additional patients who stated that they had a malignancy did not have cancer according to hospital records. The reasons for the discrepancies are not clear. In certain situations, the next-of-kin rather than the patient may have been informed of the cancerous condition. The findings indicate a need for documentation of the extent of accuracy of personal medical histories. (8 refs)

- 1075 **Malignant Neoplasm Mortality in Different Zones of a Central Italian Region: The Mountains, Hills and Coast of the Marche.** (Eng) Mastrandrea, V. (Istituto di Igiene dell' Università di Camerino, Camerino 62032, Italy); La Rosa, F.; Pannelli, F.; Cresci, A. *Zentralblatt für Bakteriologie [Orig A]* 165(3/4): 269-282; 1977.

The distribution of mortality from malignant neoplasms by individual tumor site was studied for the mountain, hill, and coastal zones of the Marche region in Italy. Based on their demographic and socioeconomic characteristics, the respective zones can be considered rural, semiurban, and urban. For men, the highest age-standardized death rates from tumors of the respiratory system, genital organs, and all sites were found in the coastal zone; the lowest rates for these tumors were found in the mountain zone. For tumors of the digestive system, the opposite findings were observed. Death rates in the hill zone were between those of the coast and the mountains. The death rates for tumors of the urinary tract were slightly higher in the hill zone than in the other two. For women, the distribution of mortality by site was similar to that seen in men, but the differences among the zones were smaller. Excluding breast cancer, male mortality was always higher than female mortality. Significant positive correlations were found between demographic size of the municipalities and tumors of the respiratory system and genital organs. For men, tumors as a whole were statistically correlated with demographic size. A decrease in digestive tract tumors was noted with increasing demographic size of the municipalities, but the trend was not significant. (26 refs)

- 78-1076 **Variation in Cancer Mortality in Chiba Prefecture - Correlation Between Different Cancers.** (Jpn) Murata, M. (Natl. Inst. Radiological Science, Anagawa, Chiba 280, Japan); Tanaka, N.; Shimamura, K.; Fukuma, S. *Chiba Med J* 53(10): 229-240; 1977.

Geographic variations in site-specific cancer mortality in the city of Chiba, Japan, were analyzed by the principal component method, and the results were compared with those obtained for nationwide geographic variations. The first principal component ( $Z_1$ ) for Chiba correlated positively with lung and breast cancers and negatively with stomach, female esophagus, and uterine cancers. This component may be an index of urban-rural differences, which constituted the fourth component of the Chiba intracity variations. The second principal component ( $Z_2$ ) showed a linear correlation with almost all cancers, especially in men, and the third component showed a similar tendency in the nationwide variation. It is, therefore, concluded that certain factors contribute to all cancer types and to the high cancer risk of men. (15 refs)

- 78-1077 **Space-Time Clustering of Burkitt's Lymphoma in the West Nile District of Uganda: 1961-1975.** (Eng) Williams, E. H. (Kuluva Hosp., Arua, Uganda); Smith, P. G.; Day, N. E.; Geser, A.; Ellice, J.; Tukey, P. *Br J Cancer* 37(1): 109-122; 1978.

Epidemiological data related to 202 patients diagnosed with Burkitt's lymphoma (BL) in the West Nile District of Uganda during 1961-1975 were reviewed and analyzed. Significant evidence of space-time clustering of cases, first reported for the period 1961-1965, was also present during 1972-1973, but not during other periods. The patients involved in these clusters were older than the others. There was no change in the overall incidence during the study period, but there were significant changes in incidence in different counties that could not be explained as case-ascertainment artifacts. One sib pair of patients with BL was found, and there were seven instances of BL in two cousins. The period between critical exposure and the onset of BL is likely to be short (1 yr or less); otherwise, it is unlikely that either space-time clustering or seasonal variation in disease incidence would occur. (20 refs)

- 78-1078 **Epidemiology of Thyroid Cancer.** (Eng) Schottenfeld, D. (Dept. Epidemiology and Preventive Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021). In: *Head and Neck Cancer. State of the Art Conference. February 16, 17 and 18, 1976.* (St. Louis,



MO: Laryngoscope): Vol. 88, No. 1, Part 2, Suppl. 8, pp. 55-57; 1978.

Although mortality from thyroid cancer predominates in women, occult thyroid cancer noted at autopsy is about as frequent in men as it is in women. The prognosis for the clinically diagnosed disease is better in women than in men. In women, the age-specific incidence peaks at 30-34 yr and again after 65 yr; that for men shows a gradually increasing incidence with age. Most tumors arise from follicular cells, and at least medullary carcinoma arises from parafoollicular cells. Papillary carcinoma accounts for 64% of the tumors, follicular 18%, medullary 2%-3%, anaplastic 2%-3%, lymphoma 1%-2%, sarcoma <1%, and other types 10%-11%. Mortality is higher among Chinese residents of the US than among white and black residents. Thyroid neoplasia can be induced in experimental animals by irradiation and excessive production of thyroid-stimulating hormone. Thyroid irradiation in persons <20 yr old carries a far greater risk of neoplasia than similar adult exposure. Familial occurrences of medullary carcinoma, pheochromocytoma, multiple endocrine neoplasia, and differentiated carcinoma in association with goiter or neurosensory deafness indicates that genetic factors also play a role. There is also a high thyroid cancer incidence and mortality in geographic areas at risk for adenomatous or nodular goiter. (no refs.)

**78-1079 Medullary Thyroid Carcinoma in Norway. Epidemiological and Genetic Data.** (Eng) Norrmann, T. (Dept. Pathology, Ulleval Hosp., Oslo, Norway). *Acta Pathol Microbiol Scand [A]* 85(6): 775-786; 1977.

Of the 1,670 cases of thyroid carcinoma traced in Norway in the period 1960-1974, 54 were primary medullary carcinomas of the thyroid (MCT). These occurred in 33 women and 21 men, and the peak incidence was in the sixth and seventh decades. The mean MCT annual incidence rate was 0.1/100,000; the relative frequency of the tumor among thyroid carcinomas was 3.4%. The distribution of the MCT cases was significantly higher in rural areas than in urban areas and in coastal areas as opposed to inland counties. Family histories were of limited value in distinguishing between familial and sporadic MCT cases. Serum calcitonin measurements revealed hypercalcitoninemia in relatives of four probands, two of whom apparently had sporadic disease. Pedigree studies demonstrated that 15 probands were related to 1 or 2 of the others; 16 additional probands had grandparents who were born in the same rural municipality as the grandparents of 1-4 other probands. Because of the high rate of consanguineous marriages in rural areas, some of these 16 probands could represent familial cases with a common genetic origin. The pattern of inheritance in one or two families was consistent with autosomal dominance; however, in at least three other families, MCT appeared to be inherited as an autosomal recessive trait. (37 refs)

**78-1080 Cancer Epidemiology.** (Spa) Carda Aparici, J. (Instituto Nacional de Oncologia, Ciudad Universitaria, Madrid-3, Spain). *Rev Esp Oncol* 23(2): 327-33; 1976.

Cancer morbidity and mortality data for Spain are presented. In 1973, the overall cancer mortality was 85/100,000 (27,386 men and 22,202 women), which accounted for 17.9% of all deaths among men and 15.5% of those among women. In 1960, the corresponding percentages were 14% and 13.4%. (no refs.)

**78-1081 The Incidence of Malignant Tumors in the Town of Khanty-Mansiisk, USSR.** (Rus.) Bychkov, V. G. (District Hosp., Khanty-Mansiisk, USSR). *Vopr Onkol* 23(7): 58-61; 1977.

Statistical data are presented on cancer mortality in the town of Khanty-Mansiisk, USSR, for the years 1966-1975. The area is characterized by a very high incidence of opisthorchiasis due to the consumption of raw and undercooked fish. The overall cancer mortality was 348, and the average age at death was 57.3 yr. Primary liver cancer accounted for 97/348 deaths. Gastric cancer accounted for 61/348, with 52.5% being in men, and the average age at death being 59.2 yr. Lung cancer accounted for 39/348, and the average age at death was 57.8 yr. Nearly 77% of the patients were men. Uterine cancer mortality was 39/348. Pancreatic cancer was the cause of death in 27 cases, intestinal cancer in 12, breast cancer in 5, and tumors of other locations in 68. (17 refs.)

**78-1082 Incidence of Malignant Neoplasms of the Larynx in the Altai Krai During the 10-Year Period from 1961 to 1970.** (Rus) Zavarzin, A. A. (Altai Krai Clinical Hosp., Barnaul, USSR). *Vestn Otorinolaringol* 44(89); 1977.

The laryngeal cancer morbidity accounted for 1.27% of the total cancer morbidity in the Altai region during the 1961-1970 period. The incidence was significantly higher among men than among women. Most cases were found among farmers, in the age bracket 40-69 yr, and in the steppe region (no refs.)

**78-1083 Registry of Malignant Mesotheliomas of the Pleura and Peritoneum. Initial Results.** (Fr)



ntz, M. (Service de Pneumologie, Centre Hospitalier Intercommunal, 40, av. de Verdun, F 94010 Creteil, France); Menza, L.; Nebut, M.; Bignon, J. *Nouv Presse Med* 6(34): 4; 1977.

European registry of mesotheliomas has been established in order to determine exact incidence, regions with high incidence, and possible relationship between the disease and occupational or environmental exposure to industrial pollutants, as well as for follow-up of patients. After one year of operation in France, results presented by geographic location and occupation indicated that of the 224 cases thus far registered, 75% involved asbestos exposure. (6 refs.)

**1084 The Distribution of Lung Cancer in Two Canadian Cities.** (Eng) Wigle, D. T. (Cancer Research, Bureau Epidemiology, Lab. Centre Disease Control, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario K1A 0L2, Canada). *Can J Public Health* 68(6): 468; 1977.

Lung cancer mortality rates were determined in the Canadian cities of Sarnia and London, where 28% and 1.2% of the work force, respectively, is employed in petroleum refining or chemical industries. Lung cancer deaths were significantly high for London men and Sarnia women. London men had a significantly high mortality from large intestine cancer and a low mortality from bladder cancer. There was a significant excess of deaths due to ovarian cancer in Sarnia. Male lung cancer rate was significantly associated with birth in continental Europe (birth in the United Kingdom or Ireland approached statistical significance) and major lifetime occupation. Increased risks of lung cancer death were associated with guards, watchmen, and persons employed in armed forces, furniture manufacturing, rubber and plastic fabricating, motor vehicle repair shops, insurance and real estate, and barber and beauty shops. In London, excess lung cancer mortality was confined largely to residents of low-income census tracts. It is concluded that the petroleum and chemical industries in Sarnia were not associated with increased lung cancer mortality in the general population. Only a low percentage of men dying of lung cancer in Sarnia were employed in these industries. (21 refs)

**1085 Epidemiology of Chronic, Nonspecific, Pulmonary Disease in Yugoslavia.** (Ger) Goldmann, M. (Institut für Lungenkrankheiten und Tuberkulose, Sremska Kamenica, Novi Sad, Yugoslavia); Zrilic, V.; Acketa, M. *Erkr Atmungsorgane* 148(3): 284-291; 1977.

The epidemiology of chronic, nonspecific, pulmonary disease in Yugoslavia is presented based on the registry of 53%-95% of all such diseases with chest clinics in the various republics. Chronic obstructive lung disease accounts for 67% of all lung dis-

eases, bronchial carcinoma for 6%, and other chronic pulmonary diseases for 27%. Approx 31.5% of all patients with chronic obstructive bronchitis are <50 yr of age and 34.7% are between 50 and 65 yr. The reported incidence of bronchial carcinoma ranges from approx 2% in Macedonia to approx 20% in Slovenia; the estimated incidences range from approx 20% in Kosova to approx 34% in Vojvodina. The reported incidences of bronchitis, bronchial asthma, and emphysema approximated the estimated values, with the highest incidence occurring in Croatia. (no refs)

**78-1086 Comparative Epidemiology of Carcinoid and Oat-Cell Tumors of the Lung.** (Eng) Godwin, J. D. (Biometry Branch, NCI, Landow Building, Bethesda, MD 20014); Brown, C. C. *Cancer* 40(4): 1671-1673; 1977.

Oat cell carcinoma and bronchial carcinoid tumor share histologic features with the Kultschitzky cell, which indicates a possible common origin from the Kultschitzky cell for these tumors. In this view, the carcinoid represents the less malignant form and the oat cell carcinoma the highly malignant form of neoplasm. However, analysis of the 124 bronchial carcinoid tumors and 2,751 oat cell carcinomas identified in the third NCI survey showed striking epidemiologic differences between the two tumors, particularly in the low male/female ratio and lower ages for carcinoid tumor. Lung carcinoids occur in the genetic disorder of multiple endocrine adenomatosis, suggesting a genetic etiology for at least some carcinoids. This contrasts with the exogenous etiologic agents of cigarette smoking, occupational exposure, and urban domicile for oat cell carcinoma. These differences between carcinoid tumor and oat cell carcinoma indicate a markedly different process of carcinogenesis, which casts doubt on the hypothesis of a common cell precursor. (9 refs.)

**78-1087 Incidence of Bone Sarcoma in SW England, 1946-74, in Relation to Age, Sex, Tumour Site and Histology.** (Eng) Price, C. H. (Radiotherapy Centre, Bristol Royal Infirmary, Horfield Road, Bristol BS2 8ED, England); Jeffree, G. M. *Br J Cancer* 36(4): 511-522; 1977.

The age-, sex-, site-, and histological type-related incidence of bone sarcoma in southwest England between 1946 and 1974 was analyzed based on 365 cases diagnosed during that period. There was a juvenile peak in the incidence of osteosarcoma and Ewing's sarcoma, an increasing incidence in adults of fibrosarcoma and Paget's disease, and a wide dispersion of lymphoma and chondrosarcoma throughout adult life. The male/female ratio ranged from 0.73 in 1950-54 to 1.59 in 1955-59, suggesting that sex plays a role in the appearance of skeletal malignancy. There was a predilection of the long bones for osteosarcoma, fibrosarcoma, and Paget's sarcoma; chondrosarcoma, malignant lymphoma, and Ewing's sarcoma were more widely dispersed. There was a predominance



of long-bone osteosarcomas in children compared to adults. Sarcomas of the small bones of the hands and feet were uncommon. Postirradiation sarcoma appeared 2 to 17 yr after irradiation. Eleven cases of chordoma were registered, as were two cases of juxtacortical osteosarcoma. These data are discussed and compared to those for Sweden. (16 refs.)

**78-1088 Latent Carcinoma of Prostate at Autopsy in Seven Areas: Collaborative Study Organized by the International Agency for Research on Cancer, Lyons, France.** (Eng) Breslow, B. (Icelandic Cancer Registry, Post Office Box 523, Reykjavik, Iceland); Chan, C. W.; Dhom, G.; Drury, R. A.; Franks, L. M.; Gellei, B.; Lee, Y. S.; Lundberg, S.; Sparke, B.; Sternby, N. H.; Tulinius, H. *Int J Cancer* 20(5): 680-688; 1977.

A worldwide comparative study of the frequency and characteristics of latent prostatic carcinoma was undertaken in seven areas, using standardized methods and blind microscopic evaluation to reduce selection and observer bias. The morphological features of 350 latent carcinomas found in 1,327 prostates were examined. Two Chinese populations, from Hong Kong and Singapore, showed a low frequency of latent carcinoma in comparison with Swedes, West Germans, and Jamaicans; an intermediate position was found for Israelis and Ugandans. The frequency of small latent carcinomas was about 12% in all the areas investigated and did not vary with age. Rates for larger latent carcinomas increased sharply with age and showed an area-to-area variation resembling that of clinical prostatic carcinoma. The small carcinomas were almost exclusively situated in the outer half of the prostate, and latent carcinomas of all sizes were evenly distributed between the anterior and posterior halves of the prostate and the right and left sides of the outer prostatic shell. Certain disagreements in diagnosis were noted when the sections from each area were evaluated independently by a different pathologist. Most of these disagreements were resolved by rereading the sections; their occurrence had no significant effect on the geographical comparisons. (26 refs.)

**78-1089 Wilms' Tumor in New York State: Epidemiology and Survivorship.** (Eng) Griffel, M. (Dept. Preventive Medicine and Environmental Health, Univ. Iowa, Iowa City, IA 52242). *Cancer* 40(6): 3140-3145; 1977.

The incidence and survival rate for Wilms' tumor between 1950 and 1972 was determined in Erie County, New York, and 23 randomly selected counties with smaller populations. The mean age at diagnosis for all 127 patients was 3.87 yr, and it did not change with time. There was no sex predominance in this group, but a survey of another group of 433 patients indicated a male:female ratio of 0.82. The left kidney was affected in 74 cases, the right in 52 (1 uncertain); the ratio was the same in boys and girls. The annual incidence in Erie

County was 0.65/100,000 and that in the less populous counties was 0.72/100,000; these should be taken as lower limits. Of the 47 Erie County patients, 50% developed metastases and 46% did not; of the 80 rural county patients, 74% developed metastases and 26% did not. Erie County patients had an 87% 7-yr survival between 1967 and 1972, compared with 50% for the other counties. Between 1960 and 1965, the 5-yr survival rates for the respective groups were 67% and 25%; between 1950 and 1959, the figures were 26% and 23%. It is concluded that the improved survival figures for the Erie County group are the result of better treatment and care in the area hospitals. (21 refs.)

**78-1090 Esophageal Cancer Morbidity as Evidenced by the Genealogy of Patients Registered in Gur'ev (Rus) Nasipov, S. N. (Gur'ev Oblast Oncological Dispensary Gur'ev, USSR). *Vopr Onkol* 23(8): 81-85; 1977.**

Esophageal cancer morbidity was studied among the relatives of 200 esophageal cancer patients (4 generations, 2,432 persons). All patients were in the age bracket 30-80+ yr. The number of esophageal cancer cases found was 254, vs an expected incidence of 117 cases. There was no esophageal cancer morbidity in 67 families. The morbidity was higher than that of the general population in only 50.5% of the families investigated. The morbidity of first-generation relatives born in the 19th century was practically the same as that of the general population. There were 165 cases among children and parents of cancer patients (expected, 60.8), 29 cases among grandparents and siblings (expected, 25.6) and 60 cases among other relatives (expected, 30.6). The morbidity was highest (3.5 times the morbidity in the general population) among spouses of the cancer patients, which indicates common environmental rather than hereditary factors. (9 refs.)

**78-1091 Retrospective Study of Carcinoma of the Esophagus in Kenya.** (Eng) Gatei, D. G. (Dept. Pathology, Univ. Nairobi, Kenya); Odhiambo, P. A.; Orinda, D. A.; Muruka, F. J.; Wasunna, A. *Cancer Res* 38(2): 303-307; 1978.

A clinical, radiological, histological, and geographical study was undertaken of carcinoma of the esophagus in Kenya. The analysis is based on a retrospective study of 667 cases from 1968 to 1975. High incidence areas were noted to be West Kenya (46%) and Central Kenya (44%). The largest number of patients was in the 50-59-yr age group and there was a male predominance of 8:1. The middle and lower thirds of the esophagus were most common sites. Squamous cell carcinoma accounted for 94.5% of the cases. There was an apparent tendency for the poorly differentiated subtype to be in the lower third of the esophagus. No correlations were observed between the degree of differentiation and age, sex, or ethnic group. Although alcohol has been suggested else



as the main etiological agent, it does not explain the striking geographical and ethnic variations in the pattern of disease in Kenya where the tribal customs and dietary habits of the West and Central Kenya are distinctly dissimilar. Preliminary epidemiological findings show a direct relationship between incidence and rainfall, which is opposite to findings in the Caspian Littoral of Iran, another area of high incidence. (14 refs.)

**78-1092 Cancer of the Colon: 32 Years of Experience in Bombay, India.** (Eng) Jussawalla, D. J. (Tata Memorial Hosp., Bombay 400 012, India); Gangadharan, P. *Surge Oncol* 9(6): 607-622; 1977.

A review of 555 cases of colon cancer seen at the Tata Memorial Hospital between 1941 and 1972 is presented. There were 384 men with an average age of 50.88 yr and 171 women with an average age of 52.20 yr. A comparison of the cancer incidence in Hindus, Moslem, Christians, and Parsis indicated that the Parsis had the highest incidence of intestinal and rectal cancer. This group also tends to be more westernized in its living and eating habits than the other groups. The age-adjusted rate in Parsi men was twice that in other groups, and the rate in Parsi women was 4.7 times higher. The Parsis had a predominance of tumors in the sigmoid region, the site of most of the tumors in the series (28%). Approximately 80% of the tumors were adenocarcinomas, 13% colloid cancers. Of the 233 resected cases, 50% survived for 5 yr, 40% for 10 yr. There was a second cancer present in 18 of these cases, most commonly in the gastrointestinal tract (8) and skin (5). A literature review on colon cancer in other countries is also presented. It is suggested that the diet, which consists of large amounts of unrefined carbohydrates, leafy vegetables, and small amounts of animal proteins and fats, contributes to the low colon cancer rate in India. The presence of intestinal parasites, leading to more frequent bowel movements, could also play a role in the etiology. (28 refs.)

**78-1093 Malignant Gastric Tumors in East Germany.** (Ger) Berndt, H. (Klinik für innere Medizin, Bezirkskrankenhaus, Postfach 480, DDR-20 Neubrandenburg, Germany); Berndt, R.; Gregor, M.; Langer, T.; Pleissner, R. *Dtsch Z Verdau Stoffwechselkr* 37(3): 123-131; 1977.

Statistical data are presented on the malignant gastric tumors that occurred in East Germany during 1956-1975. The incidence (per 100,000 inhabitants) for 1968-1972 was 52.1 for men and 35.1 for women, and it peaked in the age bracket 60-70 yr in men (369.9) and in the age bracket 80-85 yr in women (199.5). The mortality (per 100,000) was 46.8 for men and 32.6 for women; it was highest in the age bracket 75-80 yr in men (359.9) and in the age bracket 80+ yr in women (104.4). From 1962 to 1970, the mean annual incidence was 26.7/100,000 men (ranging from 45 to 63.6 in the different

counties) and 26.7/100,000 women (22.3-32). Environmental factors such as nutrition and urbanization probably are involved in the etiology of these tumors. The mean annual incidence increased from 1956 to 1960 (from 52.8 to 58.6 in men and from 26.3 to 29.2 in women), but there has been a steady decline since 1965 (from 54.3 to 47.8 in 1973 in men and 27.4 to 22.4 in women). Mortality has declined steadily since 1956 (61.8 vs 40.2 in 1975 in men and 32.3 vs 19.8 in women). (14 refs.)

**78-1094 Estimation of the Incidence, Prevalence, and Average Duration of Preclinical Gastric Cancer.** (Jpn) Hiraoka, T. (Dept. Mass Examination Gastric Cancer, Center Adult Diseases, Higashinari-ku, Osaka 537, Japan); So, K.; Umeda, K.; Oshima, A. *Jpn J Cancer Clin* 24(1): 33-40; 1978.

Gastric cancer was found in 407/89,150 persons examined radiologically from 1961 to 1974. The average duration of early gastric cancer was 1 yr for both sexes and all age groups, except for women in their 50's (1.4 yr). The average duration of advanced gastric cancer was 1-1.7 yr in men and 1.5-1.7 yr in women aged 40-60 yr. (12 refs)

**78-1095 The Recession of Gastric Cancer and Its Possible Causes.** (Eng) Seely, S. (3 Truro Drive, Sale, Cheshire, M33 5DF, England). *Med Hypotheses* 4(1): 50-57; 1978.

The hypothesis that excessively hot drinks constitute an important risk factor in the causation of gastric cancer is reexamined. In the US mortality from gastric cancer decreased by 65% between 1935 and 1971. Other countries, such as New Zealand, Australia, Canada, and Finland, have experienced 50% decreases in mortality. This recession of gastric cancer mortality rates is attributed to dietary changes tending to supplant hot beverages. These changes were influenced by the appearance of domestic refrigerators, promoting iced drinks, and the popularization of soft drinks. There has been little change in mortality rates from gastric cancer in Eastern Europe, but in some countries, such as Portugal, Mexico, and Hong Kong, the rates have been rising. This is attributed to the boiling and flavoring of water because of increased pollution or in order to mask the taste of disinfectant. The socioeconomic gradient of mortality rates may be explained by several factors: (1) the metabolic rate of men engaged in physical work is higher than those in sedentary occupations, necessitating the consumption of larger volumes of water, probably a larger quantity of hot beverages; and (2) exposure to cold, which increases the consumption of hot beverages for warmth, is more likely towards the lower end of the social scale. Heavier physical work and more exposure to cold may also explain the much higher male mortality rate compared with female rates. (20 refs)



- 78-1096 Malignant Tumors of the Stomach Following Previous Surgery for Benign or Allegedly Benign Gastroduodenal Peptic Ulcer.** (Fre) Saegesser, F. (Service universitaire de Chirurgie, CHUV, Lausanne, Switzerland); Tabrizian, M. *Chirurgie* 105(9): 729-746; 1977.

In a series of 1,365 malignant tumors of the stomach, 48 were found in patients who had undergone surgery for benign or allegedly benign peptic ulcer of the stomach or duodenum. One carcinoma was found after operation according to the Kelling-Madlener technique, 6 after gastroenteral anastomosis, 1 after Billroth I, 39 (38 carcinomas and 1 Hodgkin's-type lymphoma) after Billroth II, and 1 antropyloric reticulosarcoma was seen after vagotomy with pyloroplasty. When stomach carcinoma developed during the first few years after surgery, it was found that the benign ulcer that had prompted the surgery had, in fact, been malignant. In contrast, the latent period of the stomach carcinomas averaged 25 yr after surgery for benign ulcer (34 yr after gastroenteral anastomosis). The incidence of malignant transformation was three to five times higher in the operated patients than in the general population. Tumor incidence was the same in patients operated on for gastric ulcer and in those operated on for duodenal ulcer. This indicates that the conditions created by the surgery (decrease of gastric acidity and permanent bile reflux) are responsible for the cytological changes in the gastric mucosa that facilitate the development of carcinoma. (27 refs)

- 78-1097 The Risk for Gastric Carcinoma after Partial Gastrectomy.** (Eng) Domellof, L. (Dept. Surgery, Univ. Hosp., S-901 85 Umea, Sweden); Janunger, K. G. *Am J Surg* 134(5): 581-584; 1977.

The incidence of gastric carcinoma was studied in 676 patients (481 men, 195 women) who had undergone Billroth I or II resections for benign ulcers. The observed and expected number of carcinomas in the Billroth I group were 4 and 1.6, respectively; the corresponding figures for the Billroth II group were 10 and 6.6; the differences were not significant. Thirteen of the 14 stump carcinomas were diagnosed in men. This incidence was only significant in men 12 yr or more after surgery. No significant difference in the observed:expected ratio was found in patients undergoing surgery for gastric or duodenal ulcers. However, there may be a tendency toward development of stump carcinoma in men resected for gastric ulcer at an older age. (26 refs.)

- 78-1098 Cancer Mortality among Patients with Ankylosing Spondylitis Not Given X-Ray Therapy.** (Eng) Smith, P. G. (DHSS Cancer Epidemiology and Clinical Trials Unit, Dept. Regius Professor Medicine, Univ. Oxford, 9 Keble Road, Oxford, England); Doll, R.; Radford, E. P. *Br J Radiol* 50(598): 728-734; 1977.

The causes of death among 1,021 patients with ankylosing spondylitis not treated with x-rays (untreated group) were compared with (1) those expected in a population of similar age and sex subject to the national mortality rates for England and Wales over the same period and (2) those observed in 14,000 similar patients given deep x-ray therapy (treated group). The untreated patients were diagnosed in Great Britain and Northern Ireland during 1935-1957 and followed to 1965. The men in both treatment groups appear to have had spondylitis of similar severity, as judged from their death rates from various causes, but the untreated women appear to have had a milder form of the disease. The number of deaths from cancer in the untreated group was not greater than that expected from the national death rates, and there was no death from leukemia. In the treated series the number of deaths from leukemia was significantly higher than that among untreated patients. Death from cancers of sites classified as heavily irradiated were also higher in the treated group but this difference was not statistically significant. Thus, the excess leukemia mortality in the treated patients and, possibly, the excess from other cancers are likely to be associated with x-ray treatment rather than with the disease process itself. Death rates from causes other than cancer were similar among treated and untreated patients. Modern x-ray treatment with smaller fields and lower dosage probably will carry a smaller risk of malignancy. (5 refs.)

- 78-1099 Cancer Mortality in a Region with Endemic Nephropathy.** (Eng) Stojanov, I. S. (Inst. Oncology Medical Acad., 1156 Sofia, Bulgaria); Stojchev, I. I.; Nicolov, I. G.; Draganov, I. V.; Petkova-Bocharova, T. K.; Chernozemsky, I. N. *Neoplasma* 24(6): 625-632; 1977.

A comparison was made of the 1965-1974 cancer mortality rates in villages endemic and nonendemic for nephropathy in the same region. In all the villages studied, total mortality rates and mortality from cancer at all sites were comparable to European and world standards, with the exception of urinary system tumors in the endemic villages. In endemic villages, age-adjusted mortality rates for cancer of the kidney were 16.8/10<sup>5</sup> population for men and 14.0 for women; and for cancer of the urinary bladder, the values were 7.1 and 10.2, respectively. These rates are three to four times higher than those found in countries with high mortality rates for cancer of the urinary system. A very close correlation was observed between mortality from urinary system tumors and the incidence of endemic nephropathy, although endemic and nonendemic villages border each other and are very similar environmentally and culturally. (8 refs)

- 78-1100 Familial Aggregation of Urinary System Tumors in a Region with Endemic Nephropathy.** (Eng) Chernozemsky, I. N. (Inst. Oncology, Medical Acad.



a 1156, Bulgaria); Petkova-Bocharova, T.; Nikolov, I. G.; Ivanov, I. S. *Cancer Res* 38(4): 965-968; 1978.

distribution of urinary system tumors (UST) was studied in nine villages in the Vratza district of Bulgaria, a region endemic nephropathy. A total of 193 patients with UST were diagnosed between 1965 and 1976, and 32 of these had more than one tumorous site within the urinary system. A tendency toward familial aggregation was noted when the patients were compared with patients with malignant tumors other than UST and with healthy persons. This tendency was observed in all relatives who lived together as well as in those separated by blood. The probability of a patient with a UST having a relative with this type of tumor was 2.5 times higher than would be expected on the basis of chance alone. The patients also had significantly more relatives with endemic nephropathy than did the controls. The common occurrence of UST and nephropathy in this region could be a clue to their common etiology. (23 refs)

1101 **Bloom's Syndrome. V. Surveillance for Cancer in Affected Families.** (Eng) German, J. (310 E. 67 St., New York, NY 10021); Bloom, D.; Passarge, E. *Genet* 12(3): 162-168; 1977.

Current data in the Bloom's Syndrome Registry are summarized. Increased frequency of sister chromatid exchanges observed may be specific to this syndrome. The 71 known affected individuals represent 59 families. Follow-up is continuing on 57 of 59 living patients (av age 16.4 yr) and 58 of 59 families. Among 66 cases with data available for cancer surveillance, 13 cancers have been diagnosed to date; 7 had recognized Bloom's syndrome at the time of diagnosis, and 5 had the two diagnoses made almost simultaneously. Thus the cancer incidence in those who survived infancy was 1/5.1 persons. The av age at diagnosis of cancer was 17.4 yr. Almost half the patients developed leukemia, which appeared at an earlier age than solid tumors. Other tumors included squamous cell carcinoma, adenocarcinoma, and lymphoma. Bloom's syndrome appears to carry the greatest predisposition to cancer of all the known recessively transmitted disorders in man with the exception of skin cancers in xeroderma pigmentosum. (28 refs.)

1102 **The Incidence of Genetic Disease and the Impact on Man of an Altered Mutation Rate.** (Eng) Hubble, B. K. (Dept. Medical Genetics, Univ. British Columbia, Vancouver, British Columbia V6T 1W5, Canada); Hubble, M. E. *Can J Genet Cytol* 19(3): 375-385; 1977.

Available data on the naturally occurring frequencies of chromosomal genetic diseases (eg, neurofibromatosis and multiple polyposis coli) are used in an attempt to determine the proportion of genetic disease is mutation-maintained.

Data from two studies indicate that the frequency of non-chromosomal hereditary disease ranges from 5.20 to 9.24/100 live births. (16 refs.)

78-1103 **Blood Groups in Cancer in Assam.** (Eng) Baruah, B. D. (Dept. Pathology, Assam Medical Coll., Dibrugarh, Assam, India); Gogoi, B. C. *Indian J Cancer* 14(1): 6-9; 1977.

The association between blood group and cancer was studied in 1,108 patients with malignant tumors. A statistically non-significant increase in cancer was noted in group A and AB patients. When blood groups were analyzed according to site of cancer origin, a significant association was observed between blood group B and oropharyngeal tumors. These are compared with associations found in the literature. (24 refs.)

78-1104 **Hodgkin's Disease in an Isolated Newfoundland District (Meeting Abstract).** (Eng.) Marshall, W. (Memorial Univ. Newfoundland, St. John's, Newfoundland, Canada A1B 3V6). *Am J Epidemiol* 106(3): 249; 1977. (no refs.)

78-1105 **HBsAg-positive Chronic Liver Disease Associated with Cirrhosis and Hepatocellular Carcinoma in the Senoi.** (Eng) Sumithran, E. (Dept. Pathology, Faculty Medicine, Univ. Malaya, Kuala Lumpur, Malaysia); Prathap, K. *Cancer* 40(4): 1618-1620; 1977.

Autopsy and clinical data show that primary hepatocellular carcinoma (PHC) is the most common cancer among the Senoi, a Malaysian aborigine group. The other aborigine tribes do not appear to have this high predilection for liver cancer. PHC was present in 10/22 Senoi patients with cirrhosis. All 22 livers contained hepatocytes that stained with Shikata's orcein stain and specific immunoperoxidase and immunofluorescent stains for hepatitis B antigen (HBsAg). This suggests the possibility that hepatitis B may be an important etiologic factor in the development of cirrhosis and PHC in the Senoi. The reason for the high susceptibility of the Senoi for HB virus infection is not clear, and the role of aflatoxin in the pathogenesis of PHC in the Senoi has yet to be determined. (13 refs.)

78-1106 **Cancer Patterns in Tri-cultural New Mexico (Meeting Abstract).** (Eng.) Buechley, R. W. (Cancer Res. and Treatment Center, Sch. Medicine, Univ. New Mexico, Albuquerque, NM 87131); Kay, C. R. *Am J Epidemiol* 106(3): 251; 1977. (no refs.)



- 78-1107 Cancer of the Oral Cavity in Nigerian Igbo.** (Eng) Onuigbo, W. I. (Pathology Dept., General Hosp., Enugu, Nigeria). *ORL* 39(4): 247-250; 1977.

A review of 31 biopsy specimens from Igbo patients with cancer of the oral cavity is presented. The specimens were from the gingiva (21), palate (5), tongue (3), floor of the mouth (1), and an unspecified site (1). Burkitt's tumor (6/31) was limited to the gingiva, and it affected older rather than younger patients. There was no sex predominance with squamous cell carcinoma. It is suggested that oral cancer is not a problem with the Igbo. (16 refs.)

- 78-1108 Skin Tumours in White South Africans. Part II. Age and Sex Distribution.** (Eng) Whiting, D. A. (Dermatology Section, Dept. Internal Medicine, Southwestern Medical Sch., Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas TX 75235). *S Afr Med J* 53(4): 131-133; 1978.

The incidence of skin tumors in white South Africans was analyzed according to age and sex. The peak incidence of sun-induced tumors was in persons 50-69 yr of age. Half of the malignant melanomas were seen at ages following the decline in incidence of junctional and compound nevi. Squamous cell carcinomas occurred a decade earlier in men, probably as a result of excessive sun exposure. Spider angiomas were seen a decade later in women, reflecting their increased incidence in pregnancy. Histiocytomas occurred earlier in women. Tumors that occurred predominantly in men included squamous and all basal cell carcinomas, keratoacanthoma, and granuloma pyogenicum. Histiocytomas and spider angiomas were seen more frequently in women. (1 ref.)

- 78-1109 Racial Variation in the Incidence of Ovarian Cancer in the United States.** (Eng) Weiss, N. S. (Dept. Epidemiology, Sch. Public Health and Community Medicine Univ. Washington, Seattle, WA, 98195); Peterson, A. S. *Am J Epidemiol* 107(2): 91-95; 1978.

The incidence of ovarian cancer was determined in four US populations of heterogeneous racial-ethnic composition (Japanese, Chinese, Hispano, and black) and compared with that in white women. The epithelial tumor rates in the four racial-ethnic groups were 19%-42% lower than those in white women. Although these differences were due primarily to lower rates of serous and papillary tumors, all but the Chinese women also had a decreased incidence of mucinous tumors, and Hispano and black women had low rates of endometrioid-clear cell malignancy. The less common nonepithelial tumors (primarily dysgerminomas, teratomas, and granulosa cell carcinomas) showed no consistent pattern, and the rates for all groups were approx the same. The wide confidence limits around the ratios make all but the strongest relationships difficult to interpret. (8 refs)

- 78-1110 Medical-Genetic Survey of Two Dariusle Hutterite Colonies in Alberta (Meeting Abstract).** (Eng) Fowlow, S. B. (Div. Medical Biochemistry, Univ. Calgary, Calgary, Alberta, Canada); Church, R. *Can J Genet Cytol* 19(3): 572-573; 1977. (no refs.)

- 78-1111 Breast Cancer and Religion in Greater Bombay Women: An Epidemiological Study of 21 Women over a 9-year Period.** (Eng) Jussawalla, D. J. (Bombay Cancer Registry, Indian Cancer Society, Parel, Bombay 400 012, India); Jain, D. K. *Br J Cancer* 36(5): 634-638; 1977.

During the 9-yr period 1964 to 1972, breast cancer was diagnosed in 2,130 Bombay women, with break-down by religion as follows: Hindus (1,259), Muslims (306), Christians (26), Parsi (Zoroastrians) (226), Jains (25), Buddhists (26), and others (24). The av annual age-adjusted incidence rates were 48.5 and 18.2/100,000 in the Parsis and non-Parsis, respectively, with an av of 19.9/100,000 for the total population. For reasons not yet clear, the incidence rate in Parsis of every age group was two to three times higher than in the non-Parsis. Time-trend analyses of the data did not reveal a statistically significant increase or decrease in the incidence of breast cancer in any particular age group. Data from death certificates for the same 9-year period show that the age-adjusted mortality rate is 9.2/100,000/year. (7 refs.)

- 78-1112 Marriage and Childbearing in Relation to Cervical Cancer.** (Eng) de Graaff, J. (Dept. Obstetrics and Gynecology, Vrije Universiteit, Amsterdam, Netherlands); Stolte, L. A.; Janssens, J. *Eur J Obstet Gynecol Reprod Biol* 7(5): 307-312; 1977.

The association between marriage and childbirth and cervical cancer was investigated in 371 patients (and 192 matched controls) seen between 1950 and 1955 and 497 patients (200 controls) seen between 1960 and 1965. There was a statistically significant smaller proportion of single women in the cancer group than in the control group. The cancer patients married at a younger age than controls, and there was a consistently smaller proportion of nulliparous married women in the cervical cancer group. Furthermore, the patients delivered their first child at a markedly earlier age than controls. In the same age groups at marriage, there were more illegitimate children in the cancer group than in controls. When patients with illegitimate children were excluded, there was no difference between the groups in the time between marriage and first childbirth. In the 20- to 24-yr age group at first birth, fewer cervical cancer patients were married than controls. It appears that nulliparity has a protective influence against cervical cancer, but childbearing, regardless of the number of children, enhances the risk. (9 refs.)



- 113 **Marriage and Childbearing in Relation to the Occurrence of Endometrial Cancer.** (Eng) de Vries, J. (Dept. Obstetrics and Gynecology, Vrije Universiteit, Amsterdam, Netherlands); Stolte, L. A.; Janssens, J. *J Obstet Gynecol Reprod Biol* 7(5): 313-317; 1977.

association between marriage and childbirth and endometrial cancer was investigated in 193 patients (and 82 matched controls) seen between 1950 and 1955 and 282 patients (127 controls) seen between 1960 and 1965. Between 1950 and 1965, there was a greater number of unmarried women in the cancer group than in the control group; this was not found in the earlier groups. There was no difference in age at marriage between the endometrial cancer patients and the controls. There was a consistently larger number of parous married women in the cancer group than in the control group. The number of children did not appear to have an effect on risk. There was no difference in the age at first marriage between the groups. Apparently, there is a relationship between endometrial cancer and childless married women and not unmarried women. (10 refs.)

- 114 **Cancer Epidemiology. Series No. 5: Cancer of the Uterus in NSW.** (Eng) Ford, J. (Registrar, Central Cancer Registry, Health Commission of NSW, GPO Box 4235, Sydney, NSW 2001, Australia). *Cancer Forum* 21: 419-421; 1977.

Incidence of new cases of uterine cancer in New South Wales, Australia in 1972 is reported. There were 324 new cases of invasive cancer of the uterine cervix and 293 new cases of cancer of the corpus uteri. These figures each corresponded to 6% of all new cancers and were third and fourth, respectively, in overall incidence by leading sites among males. For in situ cancer (346 cases), the age incidence ranged from 10 to 79 yr with a peak at 30 to 39 yr; for invasive cervical cancer it ranged from 10 to 80+ yr with a peak at 50 to 59 yr; and for cancer of the corpus uteri it ranged from 10 to 80+ yr with a peak at 60 to 69 yr. Squamous cell carcinoma was the predominant type of cervical cancer (81%), while adenocarcinoma was diagnosed in 71.0% of cancers located in the corpus uteri. (no refs.)

- 115 **Clinicoepidemiologic Study of Uterine Cancer: Comparative Aspects of the Endometrial and Cervical Sites.** (Eng) Sharon, Z. (Dept. Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, Israel); Modan, M.; Modan, B. *Obstet Gynecol* 50(5): 536-540; 1977.

Newly diagnosed cases of cervical and endometrial carcinoma in Israel during the 5-yr period 1961-1965 were reviewed, and mean annual incidence rates of 4.9/100,000 and 10.0/100,000, respectively, were found. Cervical cancer was more prevalent in Moroccan-born women and among divorcees. The risk of endometrial cancer was highest for older,

European-born, and single women, but it also appeared earlier in life. Postmenopausal bleeding was the most frequent first symptom at both sites. Fifty percent of the patients of both groups were diagnosed within 1 mo, but the delay was somewhat longer in the endometrial group. Median survival was 5 yr in patients with cervical cancer and > 12 yr in those with cancer of the corpus. The 5-yr survival was 50% and 75%, respectively. Survival tended to be better in younger patients in both groups. The gradual disappearance of intra-ethnic differences in Israel are expected to lead to a decrease in the incidence of invasive cervical cancer and an increased incidence of endometrial cancer. (16 refs.)

- 78-1116 **An Epidemiologic Study of Cancer of the Cervix, Vagina, and Vulva Based on the Third National Cancer Survey in the United States.** (Eng) Henson, D. (Lab. Pathology and Biometry, Building 10, Room 2A-29, NIH, Bethesda, MD 20014); Tarone, R. *Am J Obstet Gynecol* 129(5): 525-532; 1977.

All cases of invasive and in situ carcinoma of the lower female genital tract reported in the third NCI survey (1969-1971) were analyzed by age, race, and geographic distribution. The incidence rates of in situ and invasive cervical carcinoma were greater in black than in white women, with a relative risk rate for black women of approx 2 for both types of cervical carcinoma. For white women, the age-specific rates for invasive cervical carcinoma remained relatively constant after age 45, but for black women these rates continued to increase after age 45. For both races, the patterns of age-specific incidence rates for in situ and invasive cervical carcinoma were different from those for carcinoma of the vagina or vulva. The pattern of age-specific incidence rates for cervical adenocarcinoma did not resemble those of in situ or invasive squamous cell cervical carcinoma, but it was similar to that of intraductal breast carcinoma. It has been postulated that cancers of the cervix, vagina, and vulva develop in response to the same carcinogenic stimulus. Assuming this theory is valid, the data indicate that response of these organs to the same stimulus varies with age and that the response rate of the cervix is more rapid than that of the vulva and vagina. (15 refs.)

- 78-1117 **Reserpine and Breast Cancer: A Longitudinal Study of over 2,000 Hypertensive Women (Meeting Abstract).** (Eng.) Labarthe, D. R. (Mayo Clinic, Rochester, MN 55901); O'Fallon, W. M. *Am J Epidemiol* 106(3): 251; 1977. (no refs.)

- 78-1118 **Risk Factors in Breast Cancer.** (Ger) Sachs, H. (Universitäts-Frauenklinik Hamburg, Ham-



burg, W. Germany); Ziegler, R.; Probst, P. *Fortschr Med* 95(41): 2497-2503; 1977.

Risk factors in breast cancer were formulated based on 200 breast cancer cases and 101 gynecological control cases. Postmenopausal breast cancer patients had a significantly higher concentration of  $\beta$ -lipoproteins in the blood than controls. There was no correlation between age, height, wt, and blood pressure and  $\beta$ -lipoprotein concentration. There was often a family history of breast cancer in the cancer patients. The disease had two age peaks of occurrence: one at 43 yr and another at 60 yr. These patients usually had menarche at age 14 or later and a later onset of menopause than controls. In addition, they were nulliparous or had fewer children than controls. Postmenopausal cancer patients were usually > 24 yr old at first parity; most of the women who had never breast-fed belonged to this group. A history of mammary disease was common for postmenopausal patients. Long-lasting nipple discharge before diagnosis was seen more often in the cancer patients. More than 90% of the breast cancer patients had worked and for longer periods than controls. The incidence of axillary lymph node metastases in the pre- and postmenopausal groups was 67% and 74%, respectively. The value of these risk factors should be considered in screening programs. (69 refs.)

**78-1119 A Retrospective Study of Risk Factors Related to Oral Cancer in Women (Meeting Abstract).** (Eng.) Hayes, R. B. (Johns Hopkins Univ., Sch. Hygiene and Public Health, Baltimore, MD 21205); Matanoski, G. M.; Bross, I. D. *Am J Epidemiol* 106(3): 230; 1977. (no refs.)

**78-1120 Dentition, Diet, Tobacco, and Alcohol in the Epidemiology of Oral Cancer.** (Eng) Graham, S. (Dept. Social and Preventive Medicine, State Univ. New York at Buffalo, Buffalo, NY 14214); Dayal, H.; Rohrer, T.; Swanson, M.; Sultz, H.; Shedd, D.; Fischman, S. *J Natl Cancer Inst* 59(6): 1611-1618; 1977.

The role of dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer was investigated in 584 men with histologically confirmed oral cavity cancers and 1,222 control men with nonneoplastic diseases. The risk of cancer increased from unity for patients who never smoked to 5.64 in those who were heavy smokers. Similar risks were observed for alcohol consumption: from unity at < 1 drink/wk to 2.66 for  $\geq 14$  drinks/wk. Evaluation of risk with respect to dentition indicated a risk of unity with adequate posterior and anterior dentition; this risk increased to 4.62 for inadequate total dentition. These risk factors appeared to be synergistic. The highest risk was observed for heavy smokers and drinkers with poor dentition (7.68). (18 refs.)

**78-1121 The Age Distribution of Human Cancer for Carcinogenic Exposures of Varying Intensity** (Eng) Whittemore, A. S. (Dept. Statistics, Stanford Univ. Stanford, CA 94305). *Am J Epidemiol* 106(5): 418-432; 1977.

A method of calculating time- and age-dependent incidence rates of carcinogen-induced cancers is presented, and the predictions obtained with this model are compared with observed cancer incidence rates. Carcinogen exposure is considered as effecting one of the cellular changes leading to malignant transformation. Predictions are given for constant exposures independent of or dependent on age and time, exposures of varying intensity that begin or end at particular time, and single exposures. When background exposure rates are high and exposure is fairly constant, the most significant number of excess cancers should occur among the elderly. With the adjustment allowed by this model, there is no need to restrict epidemiologic studies to the young as long as background mechanisms are involved in carcinogenesis. (19 refs.)

**78-1122 Contact with Hospital, Drugs, and Chemicals as Aetiological Factors in Leukemia.** (Eng) Timonen, T. T. (Dept. Medicine, Univ. Oulu, 90220 Oulu, Finland); Ilvonen, M. *Lancet* 1(8060): 350-352; 1978.

Two groups of patients, 45 adults with acute leukemia and chronic myeloid leukemia and 45 controls (patients without blood or other malignant disease), were questioned about the people they had had close social contact with before their illness and about their use of drugs and chemicals. Eighteen of the leukemia patients (LP) and 6 of the controls had had close social contact with hospital personnel or leukemia patients, and the difference was statistically significant ( $p < 0.01$ ). Eight of the 18 LP, but none of the controls, had been in close contact with hematological ward personnel ( $p < 0.01$ ). Nine of the 18 LP and 4/6 controls lived in the same house as healthy persons working in a hospital. Fourteen LP but only 4 controls had used drugs possibly toxic to the bone marrow ( $p < 0.01$ ), and 9 LP and 7 controls had handled chemicals (weed killers or insecticides) containing a benzene ring known to be leukemogenic. No conclusion could be drawn from the differences in drug use between the two groups, since the possibility that they were used to treat the initial symptoms of leukemia could not be excluded. (19 refs.)

**78-1123 A Study of Trends in Upper Arm Soft Tissue Sarcomas in the State of Connecticut Following the Introduction of Alum-Adsorbed Allergenic Extracts** (Eng) Jekel, J. F. (Dept. Epidemiology and Public Health, 60 College St., Yale Univ. School of Medicine, New Haven, CT, 06510); Freeman, D. H.; Meigs, J. W. *Ann Allergy* 40(1): 28-31; 1978.



incidence of upper arm soft tissue sarcomas in Connecticut between 1935 and 1974 was studied to determine if the induction of an alum-absorbed allergenic extract in 1963 had any effect. No changes were observed that could be attributed to this extract. (3 refs)

**24 Asbestos-induced Laryngeal Carcinoma.** (Ger) Bittersohl, G. (Betriebspoliklinik, VEB Leuna-Nord, "Walter Ulbricht", 422 Leuna, Lilienweg 16, E. Germany). *Z Gesamte Hyg* 23(1): 27-30; 1977.

A study was made of the association between carcinoma of the larynx and exposure to asbestos in the district of Chemnitz between 1966 and 1975. During this period, 49 patients (45 men, 5 women) were diagnosed with tumor of the larynx (38), epipharynx (8), and hypopharynx (3). Histologically, there were 2 leukoplakias of the vocal cords, 19 cornified squamous cell Ca's, 24 cornified squamous cell Ca's, 1 partially cornified squamous cell and adenoid Ca, 2 adenoid Ca's, and 1 lymphosarcoma. Five patients also presented with other primary Ca's (1 bronchial Ca, 1 rectal Ca, 1 melanocytoblastoma, 1 stomach and prostate Ca, and 1 thyroidal and prostate Ca). Forty-four of the men and 2 of the women smoked (1-40 cigarettes/day). Nineteen of the patients were previously exposed to asbestos for 8-21 yr. The time between beginning of exposure to clinical detection of the tumor was an av of 43 yr. Upon x-ray exam, 53% of the light smokers had signs of pleural hyalinosis, some with calcareous infiltrates. No abnormalities were seen in 16.6% of the patients, although they were also exposed to asbestos. There was no relation between squamous cell or adenoid Ca, since both were distributed equally among the smokers and nonsmokers. Further epidemiological studies are needed to establish definitive conclusions about the association between Ca of the larynx and asbestos exposure. (49 refs.)

**125 Correlation of Quantitative Asbestos Body Counts and Occupation in Urban Patients.** (Eng) Churg, A. (Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA 94305); Warnock, M. L. *Arch Pathol Lab Med* 101(12): 629-634; 1977.

Asbestos bodies were quantified in digests of lung from 252 urban patients aged > 40 yr. Of these patients, 18 had undergone resection for lung cancer and 234 had died from lung cancer (23%), gastrointestinal cancer (15%), other cancer (30%), or nonneoplastic disease (32%). The patients were assigned to six occupational categories that had been determined without knowledge of asbestos body counts. Asbestos bodies were present in the lungs of 96% of the total population. Fewer than 12% of the white-collar men and the white-collar women had > 100 asbestos bodies/g of lung. In contrast, 32% of the blue-collar men not working in steel mills or construction, 45%

of steelworkers, and 65% of construction workers had > 100 asbestos bodies/g lung. This distribution suggests that almost everyone in an urban population has some exposure to asbestos and that certain persons are subject to an additional occupational exposure. Whether low concentrations of asbestos bodies are related to disease remains to be determined. (28 refs.)

**78-1126 Cancer in Asbestos Mining and Other Areas of Quebec (Meeting Abstract).** (Eng.) Graham, S. (State Univ. New York at Buffalo, Amherst, NY 14226); Blanchet, M.; Rohrer, T. *Am J Epidemiol* 106(3): 231; 1977. (no refs.)

**78-1127 A Retrospective Epidemiological Study of Mortality at a Large Western Copper Smelter.** (Eng) Rencher, A. C. (Dept. Statistics, Brigham Young Univ., Provo, UT 84602); Carter, M. W.; McKee, D. W. *J Occup Med* 19(11): 754-758; 1977.

Death rates (1959-1969) at a Utah copper smelter, mine, and concentrator were compared with those for the state of Utah. The percentage of deaths due to all causes other than lung cancer was similar in the four study categories; 7.0% of all deaths at the smelter were due to lung cancer compared with 2.2% for the mine, 2.2% for the concentrator, and 2.7% for the state. The excess at the smelter was statistically significant. Approx age-adjusted death rates for lung cancer and for all causes combined were higher for the smelter than for the mine and the state. The av age at death for smelter workers, even for those who died of lung cancer, was nearly the same as for the mine employees. The increased risk among the smelter workers did not appear to be related to smoking. However, the smelter workers who died from lung cancer had the highest av cumulative exposure to sulfur dioxide (SO<sub>2</sub>), sulfuric acid mist, arsenic (As), lead, and copper. Stack emission data showed much higher As and SO<sub>2</sub> levels prior to 1959. (7 refs.)

**78-1128 Cancer Clustering Around a Coke Oven (Meeting Abstract).** (Eng.) Graff, W. (Dept. Family and Community Medicine, Univ. Utah, Salt Lake City, UT 84132); Lyon, J. *Am J Epidemiol* 106(3): 231; 1977. (no refs.)

**78-1129 Occupation and Prostatic Cancer (Meeting Abstract).** (Eng.) Ernster, V. (Univ. California Sch. Public Health, Berkeley, CA 94720); Winkelstein, W.; Selvin, S.; Sacks, S.; Brown, S. *Am J Epidemiol* 106(3): 231-232; 1977. (no refs.)



**78-1130 Occupational Distribution in C.O.L.D., Lung Cancer, Asthma and Sarcoidosis (Meeting Abstract).** (Eng.) Scherrer, M. (Div. Respiratory Diseases, Inselspital, Univ. Berne, Switzerland); Zeller, C. *Lung* 154(2): 137-138; 1977. (no refs.)

**78-1131 Adenocarcinomas of the Ethmoid Region in Woodworkers.** (Fre) Curtes, J. P. (Centre de pathologie professionnelle, 35000 Rennes, France); Trotel, E.; Bourdinier, J. *Arch Mal Prof* 38(9): 773-786; 1977.

Of 100 patients with tumors of the ethmoid region treated from 1964 to 1974, 36 (29 men, 7 women; median age, 61.8 yr) had primary malignant cancers originating in this region. There were 8 epidermoid carcinomas, 21 adenocarcinomas, 1 esthesioneuroepithelioma, and 5 hematopoietic tumors. Woodworking was the occupation of 13/21 patients with adenocarcinoma and 1/8 patients with epidermoid carcinoma. The average duration of exposure was 42 yr: 7/14 woodworkers were sons of woodworkers and, consequently, had been exposed to the etiological agent since infancy. In three patients, malignancy was diagnosed 26-29 yr after the end of a relatively brief occupational exposure of 6-12 yr. Two of the 22 remaining patients had worked as carpenters or wood-sawers. Survival for the adenocarcinoma patients was 71% to 1 yr and 31% to 3 yr; of the epidermoid carcinoma, 43% survived to 1 yr, 43% to 3 yr. Survival for the woodworkers was 21% at 5 yr. (64 refs.)

**78-1132 Respiratory-Cancer Clustering Associated with Localised Industrial Air Pollution.** (Eng) Lloyd, O. L. (Dept. Community and Occupational Medicine, Ninewells Medical Sch., Dundee DD1 9SY, Scotland). *Lancet* 1(8059): 318-320; 1978.

Mortality from respiratory cancer was studied in a Scottish town with a steel foundry. Between 1968 and 1974, there were 53 deaths (9 women, 44 men) due to primary respiratory cancer, 49 of which could be supported by hospital records. The deceased were occupationally heterogeneous, and the deaths could not be attributed solely to smoking. Of the 49 definite cases, 28 were found in the southeastern corner of the town in the region of the foundry. Moss bags were used to identify existing air pollutants. The lowest amounts of all metallic pollutants except cadmium were at sites far from the foundry, and the highest amounts were detected near the foundry. Radial clustering analysis revealed that the foundry was the center of the respiratory cancer clustering. (13 refs)

**78-1133 Polycyclic Aromatic Hydrocarbons in Soils of a Mountain Valley: Correlation with Highway Traffic and Cancer Incidence.** (Eng) Blumer, M. (Woods

Hole Oceanographic Institution, Woods Hole, MA 0254) Blumer, W.; Reich, T. *Environ Sci Technol* 11(12): 1084-1084; 1977.

Analyses of soils in the vicinity of a Swiss mountain town showed a correlation between their polycyclic aromatic hydrocarbon (PAH) content and their proximity to a highway. PAH contents ranged from 300 mg/kg dry soil near the highway to 4-8 mg/kg in the surrounding higher alps. The PAH composition ranged from three- to eight-membered rings and to heavily alkyl-substituted derivatives. The PAH mixture resembled those of automobile exhaust. The low values in the part of town close to industry but remote from the highway and the high values outside the town near the highway suggested a correlation between automobile traffic and soil PAH content. These results also indirectly suggest a correlation between automobile traffic and cancer mortality in this area. (8 refs.)

**78-1134 Fern Leaves and Cancer (Letter to Editor).** (Eng) Markus, R. L. (Berne, Switzerland). *Chem Eng News* 56(15): 4; 1978.

It is suggested that the high incidence of gastric cancer in Japan and Wales is related to their contact with plant ferns which contain a natural and potent carcinogen. The Japanese enjoy fern leaves in their salads. Welsh cows graze on fern leaves in the forest, and the chemical reaches the people in dairy products. (no refs)

**78-1135 Seabirds -- A Possible Environmental Factor in Gastric Cancer in Newfoundland.** (Eng) Pfeiffer, C. J. (Lab. Investigative Gastroenterology, Faculty Medicine Memorial Univ. Newfoundland, St. John's, Newfoundland A1C 3V6, Canada); Threlfall, W. *Digestion* 16(1/2): 1-1; 1977.

The association of seabirds with gastric cancer in fishermen and in the general population was investigated regionally in Newfoundland. Cartographic plotting and correlation analyses of 23 combined regions with respect to male, female or combined sex mortality rates showed a close similarity between high-risk areas and large seabird aggregations in the southeast region of the island. Fish-processing plants are more numerous in the high-risk coastal areas, where the majority of fishermen live. Because these plants attract seabirds in search of food, they may increase the exposure of fisherman and others in the marine environment to bacteria transmitted arboviruses or to carcinogenic fungal metabolites present in seabird excreta. (13 refs.)



1136 **Hepatomas and Other Neoplasms in the Atlantic Hagfish (*Myxine glutinosa*): A Histopathologic and Chemical Study.** (Eng) Falkmer, S. (Dept. Pathology, Univ. Umea, S-901 87 Umea 6, Sweden); Marklund, Mattsson, P. E.; Rappe, C. *Ann NY Acad Sci* 298: 342-355; 1977.

General pattern of tumor incidence as related to chemical pollutants was examined in hagfish caught along the Swedish coast over a 5-yr-period. A marked decrease in the frequency of hepatomas, liver hamartomas, and hyperplastic nodules was seen. Preliminary analyses showed that the livers of fish caught in the open sea had a much lower polychlorinated biphenyl concentration than the livers of those caught along the coast. The latter also contained DDT and its metabolites. Pesticide toxins were not found in any fish. (20 refs.)

1137 **Increasing Frequency of Thyroid Goiters in Coho Salmon (*Oncorhynchus kisutch*) in the Great Lakes.** (Eng) Moccia, R. D. (Dept. Zoology, Univ. Guelph, Guelph, Ontario, Canada N1G 2W1); Leatherland, J.; Sonstegard, R. A. *Science* 198(4315): 425-426; 1977.

Thyroid goiters recently found in increasing numbers in Great Lakes coho salmon may be environmentally induced. Sexually mature salmon collected during fall spawning runs in Lakes Michigan, Ontario and Erie had overt goiter frequencies of 6.3, 47.6, and 79.5%, respectively. Data on serum thyroxine levels suggest that low iodine content in the waters is not the sole factor involved; chemical pollutants, particularly organochlorines, may be augmenting goiter development. (14 refs.)

1138 **Environmental Carcinogenesis Studies in Fishes of the Great Lakes of North America.** (Eng) Sonstegard, R. A. (Dept. Microbiology, Univ. Guelph, Guelph, Ontario, Canada). *Ann NY Acad Sci* 298: 261-269; 1977.

Investigations from 1973-76 of > 50,000 Great Lakes fish revealed epizootics of benign gonadal tumors in goldfish, carp and goldfish x carp hybrids. Older male hybrids had tumor frequencies of up to 100% in polluted waters. The frequency of epizootics of white sucker papilloma was increased to 100% in the heavily polluted Burlington Harbor of Lake Ontario. Chemical pollutants in the water may interact with environmental and genetic factors to produce these tumors. (38 refs.)

1139 **Neoplastic Disease in Bivalve Mollusks from Oregon Estuaries with Emphasis on Research on Proliferative Disorders in Yaquina Bay Oysters.** (Eng)

Mix, M. C. (Dept. General Science, Oregon State Univ., Corvallis, OR 97331); Pribble, H. J.; Riley, R. T.; Tomasovic, S. P. *Ann NY Acad Sci* 298: 356-373; 1977.

Imported oysters, *Ostrea lurida*, were planted at various locations in Yaquina Bay to monitor their mortality and to examine them histologically for any neoplastic diseases due to pollution from nearby pulp, plywood, paperboard, and saw mills. There is no evidence that a previously reported sarcomatoid neoplastic disorder occurs in significant numbers of Yaquina Bay oysters or that it caused mortality of affected bivalves. In addition, no infectious agent could be identified. (31 refs.)

78-1140 **Spontaneous Tumors in Rats of 'Rappolovo' Breeding.** (Rus) Anisimov, V. N. (Lab. Experimental Tumors, N. N. Petrov Scientific Res. Inst. Oncology, Leningrad, USSR); Aleksandrov, V. A.; Klimashevsky, V. F.; Kolodin, V. I.; Likhachev, A. Ya.; Okulov, V. B.; Pozharissky, K. M.; Savelieva, O. P. *Vopr Onkol* 24(1): 64-70; 1978.

The incidence of spontaneous tumors was estimated in 443 Rappolovo breed random-bred rats (213 males, 230 females) in an attempt to update their oncologic characteristics. More than 80% of all neoplasms developed in > 18-mo-old animals. The incidence of spontaneous tumors was greater in females than in males: 114 tumors (29 malignant) developed in 82 female rats vs 65 tumors (34 malignant) in 55 male rats. There were a total of 44 hypophyseal tumors, 28 mammary gland tumors (1 fibroma was recorded in a male rat), 41 thyroid tumors, 4 adenomas of the adrenal cortex, 1 thecal folliculoma, 2 uterine polyps, 25 leukemias, 3 thymomas, 19 parasitogenic sarcomas, 2 skin fibromas, 2 soft tissue sarcomas, 2 hepatocellular carcinomas, 1 pancreatic adenocarcinoma, 1 salivary gland adenoma, 2 renal adenosarcomas, 1 meningioma, and 1 adenocarcinoma of the seminal vesicle. (13 refs.)

78-1141 **High Incidence of Spontaneous Transplantable Tumors in BDX Rats.** (Eng) Zoller, M. (Inst. Nuclear Medicine, German Cancer Res. Centre, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany); Matzku, S.; Goertler, K. *Br J Cancer* 37(1): 61-66; 1978.

Untreated male and female BDX rats were observed over a 30-mo period for spontaneous tumors that were subsequently transplanted into syngeneic recipients. At the age of 13-30 mo, 60/97 animals developed tumors, 53 of which were malignant, as judged by histology and/or transplantation criteria. The malignant tumors included sarcomas of connective tissue and bone; skin carcinomas; tumors of the lung, gastrointestinal tract, genitourinary tract, mammary glands, testis, and adrenal glands; sarcomas of the neural system; and



malignancies of the lymphoreticular system. Of 41 tumors implanted sc, 34 could be passaged further. With the first implant, latent periods up to 12 mo were observed; however, these periods decreased to 2-6 wk after the 4th and 5th passages. These findings indicate that the BDX rat is ideal for studies of autochthonous tumors as well as for the establishment of spontaneous tumor lines for immunological experiments. (17 refs)

**78-1142 Multiple Primary Tumors in Domestic Animals: A Preliminary View with Particular Emphasis on Tumors in Dogs.** (Eng) Priester, W. A. (Clinical Epidemiology Branch, NCI, Bethesda, MD 20014). *Cancer [Suppl]* 40(4): 1845-1848; 1977.

Of the 2,611 multiple primary tumors reported to a veterinary medical data program from March 1964 through December 1974, 2,361 were in 1,062 dogs and 250 were in 120 other domestic animal species. The 604 multiple primary malignancies (two or more malignant tumors in one animal) were similarly distributed by species, with 512 in dogs and 92 in all other species combined. The total number of multiple tumors reported in dogs closely approximated a theoretic model of random distribution, but several site-pairs of tumors seemed to occur excessively; one pair (mammary tumors and tumors of internal female organs) might parallel a similar excessive occurrence in women, suggesting a possible spontaneous tumor model for the latter. (10 refs.)

**78-1143 Serial Transplantation, Histology and Cellular Kinetics of a Rat Adenocarcinoma.** (Eng) Moore, J. V. (Clinical Res. Labs., Christie Hosp., Manchester 20, England); Dixon, B. *Cell Tissue Kinet* 10(6): 583-590; 1977.

Quantitative growth and cellular kinetic data are given for the 1st and 35th-40th transplant generations of a mammary adenocarcinoma that arose spontaneously in a female John strain Wistar rat 2 wk after the birth of a litter. The volume doubling time increased with increasing size of tumor from 1.6 days at 400 mm<sup>3</sup> to 7 days at 20,000 mm<sup>3</sup>. The values for the 1st and 37th generation tumors over the range 400-8,000 mm<sup>3</sup> were 4.00 and 3.70 days, respectively. Tumors of the first transplant generation showed minimal necrosis, and they corresponded to well-differentiated papillary adenocarcinomas. However, by the 35th to 40th generations, patchy areas of necrosis were evident, and they corresponded to poorly differentiated pleomorphic tumors with stromal elements. The labeling index for first generation tumors was 13.4%, or about half the value at 40 generations (24.7%). The mitotic indices for these generations were the same, 1.4 and 1.3, respectively. Data on the median cell cycle indicated that no marked changes occurred over 34 or more generations. (20 refs.)

*See also:*

\*(Rev.): 78-0607, 78-0611, 78-0614, 78-0615, 78-0616, 78-0620, 78-0621, 78-0622, 78-0623, 78-0624, 78-0635, 78-0638, 78-0641, 78-0655, 78-0656, 78-0664, 78-0665, 78-0667, 78-0671, 78-0672, 78-0673, 78-0674, 78-0675.

\*(Chem.): 78-0695, 78-0701, 78-0702, 78-0703, 78-0744, 78-0765, 78-0767, 78-0768, 78-0790, 78-0792, 78-0794, 78-0795, 78-0806, 78-0811.

\*(Phys.): 78-0814, 78-0815.

\*(Viral): 78-0870, 78-0893, 78-0912, 78-0914, 78-0915.

\*(Immun.): 78-0974.

\*(Path.): 78-0996, 78-1011, 78-1018, 78-1019, 78-1030, 78-1039, 78-1060.



## MISCELLANEOUS

14 **Cell Walls of Crown-Gall Tumors and Embryonic Plant Tissues Lack *Agrobacterium* Adher-  
sites.** (Eng) Lippincott, J. A. (Dept. Biological Sciences,  
western Univ., Evanston, IL, 60201); Lippincott, B. B.  
e 199(4333): 1075-1078; 1978.

ility of plant cell walls to inhibit tumor initiation by  
*acterium tumefaciens* was examined. Cell walls were  
d from 7- to 21-day-old seedlings, embryonic tissues  
eds germinated for 3 days, crown-gall tumors in vivo,  
l tissues from the same plants, and normal, habituated,  
morous crown-gall tissue cultures. Samples composed  
ain B6 *A. tumefaciens* plus cell walls, B6 plus *A.*  
*aciens* avirulent site-binding strain IIBNV6-pretreated  
alls, and B6 alone were each injected on primary leaves  
o bean plants. Seven days later, the tumors were count-  
umor initiation was inhibited by cell walls from normal  
edonous plants but not by cell walls from crown-gall  
s, apparently because of bacterial adherence or nonad-  
e, respectively, to the different cell walls. Cell walls  
normal and tumor tissues in culture also showed this  
nce. Habituated tissue cultures, which resemble crown-  
umor cultures, formed cell walls that were inhibitory,  
ose of the normal cultures from which they were  
d. Cell walls from embryonic tissues were noninhibito-  
hough those from 7- to 10-day-old seedlings were in-  
ry. The lack of inhibitory activity on the part of both  
onic and tumor cell walls may be due to a similarity  
r cell wall metabolism, and it suggests that an embry-  
e cell wall metabolism is characteristic of the tumors.  
fs)

45 **Substrate Induction of Conjugative Activity of  
*Agrobacterium tumefaciens* Ti Plasmids.** (Eng)  
A. (Station de Genetique et Amelioration des Plantes,  
A., 78000 Versailles, France); Tempe, J.; Kerr, A.;  
ers, M.; Van Montagu, M.; Schell, J. *Nature* 271(5645):  
72; 1978.

tempt was made to distinguish between the models of  
tion of transfer and selection of transconjugates in  
*acterium tumefaciens* Ti plasmids. The Ti plasmids  
r oncogenicity to *A. tumefaciens* strains responsible for  
rown-gall disease of plants. Octopine induced conjuga-  
tivity in the Ti plasmid of strain B6S3. Crosses per-  
d with donors that previously had been cultured on  
ine yielded transconjugants, but donors cultivated on  
ne and pyruvate did not transfer their plasmid in the  
ce of octopine. The other opines, lysopine, nopaline, and

octopinic acid, induced conjugation, but histopine did not.  
Since the catabolism of nopaline and octopine is coded for  
by plasmid genes and is inducible by the same substrates, both  
catabolic activity and transfer activity could be under the  
control of the same system. Investigations suggested a com-  
mon regulatory gene controlling two distinct operons, one  
involved in catabolic activity and the other in plasmic trans-  
fer. Thus, conjugative activity of the Ti plasmids can be in-  
duced by the substrates of some specific enzymes coded for  
by the Ti plasmids. (20 refs)

78-1146 **Establishment of Epithelial Cell Lines from Rat  
Glandular Stomachs.** (Eng) Huh, N. (Dept.  
Cancer Cell Res., Inst. Medical Science, Univ. Tokyo,  
Shirokanedai, Minato-ku, Tokyo 108, Japan); Takaoka, T.;  
Katsuta, H. *Jpn J Exp Med* 47(5): 413-424; 1977.

Nine epithelial cell lines (RGS-2, -3A, -4A, -4B, -5, -6, -7A,  
-8, and -9) were established from the glandular stomach of  
fetal (8) and suckling (1) JAR-2 rats, and some of their prop-  
erties were investigated. Population doubling times were 25.9  
hr in RGS-4A, 28.8 hr in RGS-5, and 50.4 hr in RGS-7A  
cells. The modal chromosome number was 42 in RGS-2,  
RGS-3A, and RGS-4A after approx 1 yr of cultivation. They  
showed pseudodiploid karyotypes and lacked marker  
chromosomes. In RGS-2, the modal chromosome number  
shifted to 41 with time, and chromosome numbers were dis-  
tributed more widely. RGS-8 cells developed hemicysts when  
maintained in confluent monolayers for 3-4 wk. Hemicysts  
were also noted in RGS-5 and RGS-2, but they were not as  
numerous as those in RGS-8. Addition of 1 mM dibutyryl  
cyclic AMP (dbcAMP) plus 1 mM theophylline or 2 mM  
dbcAMP alone to the culture medium enhanced hemicyst  
formation. RGS-2 (at 11 and 22 mo after initiation) and  
RGS-3 and RGS-8 (at 1 yr after initiation) were tested for  
tumorigenicity in JAR-2 mice; no tumors were detected.  
These lines may be useful for the study of chemical carcino-  
genesis in culture. (27 refs)

78-1147 **New Tissue Culture Cell Lines Derived from  
Human Squamous Cell Carcinoma of the Cervix  
and Vagina. Squamous Cells in Tissue Culture.** (Eng) Porter,  
J. C. (Dept. Obstetrics and Gynecology, Southwestern Medi-  
cal Sch., 5323 Harry Hines Blvd., Dallas, TX, 75235); Nalick,  
R. H.; Vellios, F.; Neaves, W. B.; MacDonald, P. C. *Am J*  
*Obstet Gynecol* 130(4): 487-496; 1978.



The establishment of two human squamous cell carcinoma lines is reported. One line, EC-50, was derived from the ascitic fluid cells of a 57-yr-old woman with recurrent carcinoma of the uterine cervix. The other line, EC-82, was derived from a biopsy specimen of a 42-yr-old woman with primary vaginal carcinoma. Cells from passage 13 of EC-50 and 17 of EC-82 were tumorigenic when injected subdermally into the cheek pouches of cortisone-treated golden hamsters. The histologic pattern of the tumor grown from EC-50 cells and that of a biopsy of the original carcinoma of the uterine cervix were indistinguishable. In addition, the histologic pattern of the tumor grown from EC-82 cells was identical to that of the biopsy of the original vaginal carcinoma. At passages 54 and 72 of EC-50 and passages 47 and 70 of EC-82, sc injection of cells into nude mice produced tumors that were histologically indistinguishable from the original tumors. The chromosome number of EC-50 was 65-70 and that of EC-82 was 83-87; their doubling times were 16 and 20 hr, respectively. EC-82 produced chorionic gonadotropin. Both lines have currently undergone > 110 passages and have maintained their tumorigenicity. These lines may be useful for the study of therapeutic protocols, ectopic hormone production, and tumor-specific antigens. (18 refs)

- 78-1148 Development of an Epithelial Tissue Culture Line from Human Prostatic Adenocarcinoma.** (Eng) Lubaroff, D. M. (Dept. Urology, Univ. Iowa, Iowa City, IA 52242). *J Urol* 118(4): 612-615; 1977.

The establishment of a pure epithelial cell line (HPC-36) from a patient with prostatic adenocarcinoma is reported. Cells from this line stain positively for acid phosphatase and have many cytologic properties of neoplastic cells. Current studies will determine whether these cells are true descendants of the tumor cells. (14 refs.)

- 78-1149 Cloning of Murine Transformed Cell Lines in Suspension Culture with Efficiencies near 100%.** (Eng) Lernhardt, W. (Basel Inst. Immunology, CH-4005 Basel 5, Switzerland); Andersson, J.; Coutinho, A.; Melchers, F. *Exp Cell Res* 111(2): 309-316; 1978.

Cloning efficiencies of a series of murine T and B lymphomas and myelomas in suspension cultures were determined in the presence of filler cells either from syngeneic, allogeneic, or xenogeneic thymus or from xenogeneic peripheral lymph. Addition of  $3 \times 10^6$  thymus cells increased the cloning efficiencies of murine thymomas (EL-4, WC-2), B lymphomas (McPC 1748, 38C-13), Abelson virus-transformed cell lines (F and K), mastocytomas (P815), myelomas (AbPC22, X63-AG8, 5563, MOPC 104 E, RPC 5, W 3469), and hybrids of myelomas and normal B lymphocytes (Sp-1) to near 100%. Thymus cells also increased the efficiencies of growth initiation in primary in vitro cultures of myeloma tumor cells

(S117) transplanted in vivo and of cells fused between azaguanine-resistant X63-AG8 myeloma cell line and non-bacterial lipopolysaccharide-stimulated B-lymphocyte blastoclasts. It is not known whether mouse or rat thymus cells will support the growth of malignant or normal cells from other species, but it is clear that thymus cells from other species support the growth of mouse cells. (27 refs.)

- 78-1150 Lack of Correlation Between Plasminogen Activating Factor Production and Tumorigenicity in Rat Liver Epithelial Cells.** (Eng) San, R. H. (Naylor D. Inst. Disease Prevention, American Health Foundation, Dana Road, Valhalla, NY, 10595); Rice, J. M.; Williams, M. *Cancer Lett* 3(5/6): 243-246; 1977.

The association between plasminogen activating factor (PAF) production and tumorigenicity was investigated in seven epithelial cell lines from normal Wistar or Fischer livers and three hepatocarcinoma lines, one each from Falo, A x C, and Fischer rats. All the normal liver lines produced PAF, and two of these were tumorigenic in nude mice (incidences were 2/5 and 5/5, respectively). One tumor arising from each of these two lines regressed. One highly tumorigenic hepatocarcinoma line produced no PAF; of the three that did, only one formed tumors in nude mice. Thus, there is no correlation between PAF production and tumorigenicity. (15 refs)

- 78-1151 Test for Malignant Transformation of Rat Liver Cells in Culture: Cytology, Growth in Soft Agar, and Production of Plasminogen Activator.** (Eng) Montesano, R. (International Agency Res. Cancer, Unit Chemical Carcinogenesis, Lyon, France); Drevon, C.; Kuroki, T.; Sato, Vincent, L.; Handleman, S.; Sanford, K. K.; DeFeo, Weinstein, I. B. *J Natl Cancer Inst* 59(6): 1651-1658; 1977.

Three parameters were evaluated as diagnostic of the malignant potential of cultured rat liver epithelial cells: cytology, growth in soft agar, and production of extracellular plasminogen activator. A total of 22 tumorigenic and nontumorigenic cultures from 15 cell lines were assayed by three laboratories. Cytologic diagnosis and growth in soft agar were reliable indicators of the malignant potential of the cells. However, the production of extracellular plasminogen activator showed little correlation with tumorigenicity. Of the cytologic properties evaluated, the two that correlated best with malignant potential were increased cytoplasmic basophilia and increased nuclear:cytoplasmic ratio. (41 refs.)

- 78-1152 The Cytology of Spontaneous Neoplastic Transformation in Culture.** (Eng) Handleman, S.



chemistry Lab., NCI, Bethesda, MD 20014); Sanford, K. Arone, R. E.; Parshad, R. *In Vitro* 13(9): 526-536; 1977.

aneous neoplastic transformation was studied in cell established from 3 pools of 13-day-old C3H/HeN embryos, 1 pool of a 14-day-old Syrian hamster embryo and 3 pools of 18-day-old Fischer rat embryos. Of the 8 colonies formed, 8 underwent neoplastic transformation. The effect of serum, passage number, and proliferative activity of cultures were not related to time of transformation. Histologically, all tumors were sarcomas. The cellular criteria that related most with neoplastic transformation were cytochrome basophilia, reduced cytoplasmic spreading on subconfluent, high nuclear:cytoplasmic ratio, and clumping. The percentage of colonies classified as malignant tended to increase with onset of tumorigenicity. One rat line had relatively high percentages of malignant cells that increased continuously by the fifth culture. Cells from this line and the rat induced were all diploid, contrasting with pretransformation. Mouse cells grown in medium with horse serum had more abnormal chromosomes than those grown in medium with fetal bovine serum. This method provides a direct in vitro assay for the transformation of cells in culture. (23 refs.)

53 **Squamous Metaplasia of Human Mammary Epithelium in Long-Term Organ Culture.** (Fre) Bogaert, L. J. (Unite de Pathologie et Cytologie Experimentales, 5249 Tour Vesale, 52, avenue E. Mounier, 1200 Brussels, Belgium). *Experientia* 33(11): 1450-1451; 1977.

The incidence of squamous metaplasia in long-term organ cultures of human mammary tissue in Earle's 199 salt medium (2.2 g NaHCO<sub>3</sub>/liter) was compared with that occurring in the same medium enriched with 5 µg/ml insulin or glucose. Metaplasia occurred only in the non-enriched medium. (9 refs.)

54 **Scanning Electron Microscopic Studies on Untreated and Transformed Mouse Embryo Fibroblast Cell Cultures.** (Eng) Ferencz, G. (I. Inst. of Pathology, Semmelweis Medical Univ., Ulloi ut 26, H-108 Budapest VIII, Hungary); Szende, B.; Lapis, K.; Janiczky, E. *Exp Pathol (Jena)* 13(4/5): 275-279; 1977.

Scanning electron microscopy studies were performed on cells obtained from CBA T6T6 embryos (K culture), K-culture cells treated with 0.1 µg/ml 20-methylcholanthrene for 4 days (MC culture), and cultures obtained from spindle cell sarcomas in CBA T6T6 mice inoculated with 4 x 10<sup>6</sup> MC culture cells (MRC culture). K-culture cells showed a parallel arrangement with contact inhibition. Microvillous processes were organized on the surface, and the few cell processes

were more or less parallel. The MC cultures were multilayered with bulkier, wider, and unorganized cell processes. The dividing cells had a globular shape. The MRC cultures showed a multilayered crisscross pattern of growth. The surface appeared villous from the numerous tiny microvilli-like processes crossing each other. The surface of the globular cells preparing to divide was more uneven than the surface of the MC culture cells. These morphological changes are assumed to be characteristics of malignantly transformed cell cultures. (10 refs.)

78-1155 **Mouse Brain Extract with "Fibroblast Growth Factor"-Activity.** (Eng) Karasek, E. (Institut für Wirkstoffforschung, Akademie der Wissenschaften der DDR, Alfred-Kowalke-Strasse 4, DDR-1136 Berlin, E. Germany); Jentzsch, K. D.; Bohmer, A.; Oelssner, W.; Heder, G. *Exp Pathol (Jena)* 14(6): 328-333; 1977.

Six mouse whole-brain extracts (MBE) from NMRI or ICR mice were examined for the presence of fibroblast growth factor activity. The results were essentially the same in medium with or without serum. Small doses of MBE reduced the loss of cells caused by serum deprivation to an average of 17% of the initial cell number and 16% of the initial protein content. However, 150-300 µg/ml stimulated proliferation so that initial values were clearly surpassed. A dose of 300 µg/ml also increased average protein content/culture to 70% of that obtained in medium containing 10% calf serum. This same dose added to cells in medium containing 10% calf serum caused an additive proliferative effect. As a result of intensified cell metabolism, the mean pH of the test media decreased proportionally with increase in cell number and protein content. Addition of 0.7 µg/ml hydrocortisone reduced the proliferative effect of MBE. Two MBE preparations tested stimulated incorporation of thymidine into mouse embryo fibroblasts cultivated for 24 hr without serum. Two MBE preparations at 20-300 µg/ml failed to stimulate chicken embryo fibroblasts and L cells. It is concluded that this MBE activity is qualitatively identical to that previously detected in the brains or hypophyses of cattle. (12 refs.)

78-1156 **The Effects of Cell-Cell Contact on the Spreading of Pigmented Retina Epithelial Cells in Culture.** (Eng) Middleton, C. A. (Dept. Anatomy, Univ. Leeds, Leeds LS2 9NL, England). *Exp Cell Res* 109(2): 349-359; 1977.

Pigmented retina cells (PRC) were taken from the eyes of 10-day-old chick embryos. PRC that were incorporated into islands or sheets of cells were extensively spread upon the substrate, lacked blebs and had typical leading lamellae if marginally positioned on the island. Isolated PRC lacked leading lamellae, blebbed vigorously and were poorly spread on the substrate; within 3 hr of contact, they assumed the



morphology of an incorporated cell. It is proposed that this phenomenon resulting from cell-cell contact be termed contact-induced spreading. (20 refs.)

- 78-1157 Proliferation and Growth-related Changes in Concentration of Taurine in L1210 Leukemia Cells (Meeting Abstract).** (Eng) Baskin, S. I. (Dept. Pharmacy and Medicine, Medical Coll. Pennsylvania, Philadelphia, PA, 19129); Howell, R. R.; Steinman, H.; Smeraski, P.; Besa, E. C.; Jepson, J. H. *Fed Proc* 37(3): 680; 1978. (no refs)

- 78-1158 Membrane Microviscosity Differences in Normal and Leukaemic Human Lymphocytes.** (Eng) Johnson, S. M. (Div. Immunological Medicine, Clinical Res. Centre, Watford Road, Harrow, England); Kramers, M. *Biochem Biophys Res Commun* 80(2): 451-457; 1978.

The membrane microviscosity of normal human tonsil lymphocytes, circulating blood mononuclear cells, and human chronic lymphocytic and acute lymphoblastic leukemia cells was studied using the fluorescent probe 1,6-diphenyl-1,3,5-hexatriene (DPH). The normal tonsil and acute lymphoblastic leukemia cells did not differ significantly with respect to DPH polarization. However, both were just significantly less than chronic lymphocytic leukemia cells, which were just significantly less than the circulating mononuclear cells; these findings cannot be correlated with leukemic transformation. The plasma membranes were more viscous than whole cells, and liposomes were only 57% as viscous as the plasma membranes from which they were prepared. The polarization degree of DPH in the lymphocytes was much lower and more variable than that of DPH in the platelets, polymorphonuclear WBC, and RBC membranes. (15 refs)

- 78-1159 Evidence for a Proliferative Advantage of Human Leukemia Colony-forming Cells In Vitro.** (Eng) Broxmeyer, H. E. (Memorial Sloan-Kettering Inst. Cancer Res., Section 6136, Room 1104, Schwartz Building, New York, NY, 10021); Grossbard, E.; Jacobsen, N.; Moore, M. A. *J Natl Cancer Inst* 60(3): 513-521; 1978.

Extracts from the marrow and blood cells of leukemia patients were assayed for their inhibitory activity against normal and leukemia granulocyte-monocyte colony-forming cells in agar (CFU-C) present in fractions of nonadherent, light density bone marrow. Extracts from untreated acute leukemia patients or those in relapse inhibited the proliferation of normal CFU-U to a greater extent than extracts from patients with chronic myelogenous or chronic lymphocytic leukemia. Leukemia CFU-C were unaffected by single or multiple additions of leukemia cell extracts containing  $10^4$ - $10^6$  times as much inhibitory activity as that

required for max stimulation of normal CFU-C. Cells from acute leukemia patients in remission rarely demonstrated inhibitory activity; however, the CFU-C from these patients were insensitive to active leukemia cell extracts. The cell responsible for inhibiting normal CFU-C was nonadherent and of light density, and it had a velocity sedimentation range of 2.5-6.3 mm/hr. The relevance of in vitro CFU-C inhibition to the pathogenesis of acute leukemia is discussed. (31 refs.)

- 78-1160 An Increased Requirement for Methionine in Transformed Rat Liver Epithelial Cells In Vitro.** (Eng) Wilson, M. J. (Nutrition and Metabolism Section, Carcinogen Metabolism and Toxicology Branch, NCI, Bethesda, MD, 20014); Poirier, L. A. *Exp Cell Res* 111(2): 3400; 1978.

The growth of two normal and four transformed rat liver epithelial cell lines in a methionine-containing medium and a methionine-deficient medium supplemented with homocysteine was examined. The two normal cell lines grew to confluence on the methionine-deficient, homocysteine-containing medium and retained their morphology, but their growth was only 50% of that observed when the same cell lines were grown on a methionine-containing medium. Three of the four transformed cell lines showed virtually no growth on homocysteine-supplemented medium, although they grew rapidly on the methionine-containing medium. The fourth line, transformed by N-methyl-N-nitrosourea, grew on homocysteine-supplemented medium at one-third the rate of the cells on methionine-containing medium. Thus, transformed rat liver epithelial cells resemble other malignant cells in their reduced capacity to grow on homocysteine in the absence of methionine. (20 refs.)

- 78-1161 Effect of Vitamin A Deficiency on Intestinal Cell Proliferation in the Rat.** (Eng) Zile, M. (Dept. Biochemistry, Coll. Agricultural and Life Sciences, Univ. Wisconsin-Madison, Madison, WI 53706); Bunge, J. C.; DeLuca, H. F. *J Nutr* 107(4): 552-560; 1977.

The effect of vitamin A deficiency on the cell division kinetics and biochemical composition of the small intestine of weanling male Holtzman rats was determined. The rats were further divided into those who received no vitamin A and those who received retinol (10 or 20  $\mu$ g po every 2 days). The growth rate of the deficient rats started to decrease after they had been fed the deficient diet for 5-6 days. Within 1 wk, their wt had plateaued or decreased. At the time of sacrifice, no vitamin A could be detected in the livers of the deficient rats and their serum levels were less than one-third of normal. Grossly, the intestinal length and jejunal mucosa appeared unaffected. The generation time for the jejunal crypt cells was 1.3



er in deficient rats than in vitamin A-supplemented rats, ly as a result of an increase in the S phase by 1.5 hr. The ion of  $G_1$  and  $G_2 + M$  was not affected. The labeling of the jejunal crypts of deficient and normal rats was tially the same. However, the proportion of labeled cells e crypts of normal rats remained constant until the onset second cell division, whereas the proportion of labeled in the crypts of deficient animals increased after 1.5 hr 47% to 49% of the cells were labeled by 6 hr. There no significant difference between the two groups with et to growth fraction or overall biochemical composition e jejunal mucosa. Since vitamin A is essential for the cement of intestinal cells, the tissue of the deprived ani- may have an impaired ability to withstand exogenous es. (35 refs.)

162 **The Effects of Dietary Deficiencies of Magnesium and Potassium on the Growth and Chemistry Transplanted Tumours and Host Tissues in the Rat.** (Eng) g, G. A. (Renal Res. Unit, General Infirmary, Leeds, and); Parsons, F. M. *Eur J Cancer* 13(2): 103-113; 1977.

aling Wistar rats fed a control diet or a diet deficient in and/or K for 1-3 wk were inoculated sc with Yoshida alker tumors. Restricted intakes were given to prevent tional differences between the groups. Cation depletion assessed from plasma and muscle concentrations. Organ d tissue biochemistry showed that metabolic differences een control and cation-deficient rats were due predomi- y to cation deficiency and tumor growth, rather than nutritional deficiencies. A reduction in tumor size oc- d with Mg deficiency (up to 40%), K deficiency (30%- , and combined deficiency (45%-85%). Tumor size ed the best correlation with the combined concentra- of plasma Mg and K or muscle K. A significant reduc- in tumor K was observed only with a marked combined ency. Mg and K levels correlated in the tumor but not uscle. Dietary depletion of both Mg and K may affect plication and survival of tumor cells by inhibiting meta- activity and causing the loss of intracellular K. (19 refs.)

163 **Calcium Content and Distribution as a Function of Growth and Transformation in the Mouse Cell.** (Eng) Tupper, J. T. (Dept. Biology, Syracuse Univ., use, NY 13210); Zorngiotti, F. *J Cell Biol* 75(1): 12-22;

um content and distribution between the cell surface ntracellular environment were studied as a function of th and transformation in BALB/c 3T3 mouse cells e A31). After 7 hr of incubation, Ca uptake increased with cell growth; equilibrium with cell growth occurred d 15 hr. All studies were performed after at least 24 hr ubation. During exponential growth, the cells contained

525 picomoles (pmol) of Ca/ $\mu$ l cell volume. Approx 457 pmol/ $\mu$ l could not be removed by ethylene glycol-bis( $\beta$ - aminoethyl ether)N,N,N',N'-tetraacetate (EGTA), which removes surface Ca; this remaining value thus represents intracellular Ca. The low level of Ca removal increased with cell density until it was seven times greater at quiescence. Simian virus 40 (SV40)-transformed cells had approx two-thirds the Ca level of transformed cells, but their EGTA sensitivity was about the same as normal cells. In contrast to normal cells, the EGTA sensitivity of the transformed cells did not increase with cell density. Growth of normal cells in 4% calf serum stopped proliferation and increased EGTA-removable Ca fourfold. Similar treatment of transformed cells did not reduce growth rate or alter Ca distribution. At 0.5% medium serum levels, however, the transformed cell growth rate was reduced substantially and EGTA-removable Ca increased twofold. Apparently, an increase in cell-surface Ca is associated with growth inhibition. (21 refs.)

78-1164 **D-T Diaphorase Activity in Preneoplastic Lesions of the Rat Liver (Meeting Abstract).** (Eng) Schor, N. A. (Tulane Univ., New Orleans, LA, 70112); Ogawa, K.; Lee, G.; Farber, E. *Fed Proc* 37(3): 451; 1978. (no refs)

78-1165 **Adenosine Deaminase Activity in Hepatomas of Various Grades of Malignancy.** (Rus) Davydova, S. Ya. (Lab. Tumor Biochemistry, Cancer Res. Center, Moscow, USSR); Vetchinin, S. S. *Biull Eksp Biol Med* 85(1): 60-61; 1978.

Adenosine deaminase (AD) activity was determined in the liver and tumor tissue of random-bred albino mice with transplanted Ehrlich ascites carcinoma and C3HA mice with transplanted Gelshtein hepatomas (GH). The following GH variants were tested: the rapidly growing, extremely malignant, ascites hepatoma 22; the slowly growing, moderately malignant hepatomas 60 and 61; and the slowly growing, slightly malignant hepatoma 46. The AD activity in hepatomas 46, 60, and 61 was 5.06, 5.8, and 6.28 IU, respectively, compared to 6.69 IU in normal liver. Hepatoma 22 and the Ehrlich carcinoma had a significant (approx threefold) decrease in AD activity (2.64 and 1.94 IU, respectively). (6 refs.)

78-1166 **Activity of Enzymes of Glucose-6-phosphate Metabolism in Hepatomas with Various Growth Rates.** (Rus) Teras, L. E. (Inst. Experimental and Clinical Medicine, Tallin, USSR); Lond, M. E. *Vestn Akad Med Nauk SSSR* (10): 82-84; 1977.



The activities of hexokinase (HK), glucokinase (GK) and glucose-6-phosphate dehydrogenase (G-6-PDH), enzymes involved in glucose-6-phosphate metabolism, were assessed in the liver and tumor tissue of C3HA mice with transplanted hepatomas 46, 48, 60, 22A, 61-423, and 1676-52. HK activity was significantly increased in all hepatomas, especially in the rapidly growing hepatoma 22A. The activity was increased by a factor of 9 in this tumor, compared with 1.5 in the slowly growing hepatomas 46 and 48, and 4-6 in the rapidly growing, poorly differentiated hepatomas 60, 61-423, and 1676-52. GK activity was decreased by 30%-70% and that of G-6-PDH was increased markedly in all hepatomas, regardless of their growth rate. (8 refs.)

- 78-1167 Changes of Lactate Dehydrogenase Isozymes in Oncogenesis.** (Rus) Ageenko, A. I. (Lab. Virology, P. A. Hertsen Scientific Res. Cancer Inst., Moscow, USSR); Vitorgan, Yu. E.; Chernomordik, A. E. *Vopr Onkol* 24(1): 51-55; 1978.

The lactate dehydrogenase (LDH) isozyme pattern was assessed by polyacrylamide gel-disk electrophoresis in tumor and polyp tissue specimens obtained from 196 patients with carcinoma of the large intestine and 252 patients with polyposis of the large intestine. The cathode fractions (especially, LDH-5) were increased in 91.3% of the patients with carcinoma of the large intestine. In the polyposis patients, however, an increase in LDH-5 activity was correlated with an increase in polyp size: 38.5% of the patients with polyps < 1 cm in diameter showed no increase in LDH-5. (20 refs)

- 78-1168 Lymphocyte Surface Glycosyltransferase.** (Eng) Endres, R. O. (Dept. Microbiology, Coll. Medicine, Univ. Arizona, Tucson, AZ); Lucas, D. O. *In: Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 423-425; 1977.

In mouse spleen cells cultured for 48 hr with concanavalin A (Con A), the addition of 5 mM 5'-AMP prevented the hydrolysis of nucleotide sugars, thereby allowing incorporation at the cell surface to be detected. When three criteria for defining surface glycosyltransferase activity were satisfied experimentally, the results showed that the Con A-stimulated spleen cells lacked either the enzymes or acceptors necessary for the incorporation of galactose at the cell surface. Measurements of the incorporation from uridine diphosphate <sup>14</sup>C-galactose by Con A-stimulated mouse lymphocytes in the presence of 5'-AMP indicated that spleen cells have the necessary enzymes, but lack available surface acceptors. Con A, but not lipopolysaccharide, stimulated the incorporation of mannose from <sup>14</sup>C-mannose in the presence of 5'-AMP, which suggests that this activity may be unique to T cells. (5 refs.)

- 78-1169 Purification, Properties, and Subunit Structure of Deoxyribonucleic Acid-dependent Ribonucleic Acid Polymerase III from Uninfected and Adenovirus 2-infected KB Cells.** (Eng) Jaehning, J. A. (Dept. Biochemistry, Div. Biology and Biomedical Sciences, Washington Univ., St. Louis, MO 63110); Woods, P. S.; Roeder, G. *J Biol Chem* 252(23): 8762-8771; 1977.

Class III DNA-dependent RNA polymerase (RNA polymerase III) from uninfected and adenovirus 2 (Ad2) infected human KB cells were purified approx 14,500-32,000-fold, respectively, relative to whole cell extracts. Subunit compositions of the purified RNA polymerases were analyzed by polyacrylamide gel electrophoresis under reducing conditions. The structures of the RNA polymerases from uninfected and infected cells appeared to be identical. Each enzyme contained polypeptides with mol wt of 155,000, 138,000, 86,000, 63,000, 13,000, 34,000, 32,000, 27,000, 22,000. Molar ratios were close to unity for all subunits except the 22,000-mol wt peptide, which was present in a ratio of from 2 to 3 in different preparations. Comparative structural studies with class III enzymes from *Xenopus* oocytes and the mouse plasmacytoma, MOPC 315, revealed striking similarities in subunit composition as well as slight differences. Partially purified RNA polymerases from infected cells was used to transcribe purified, intact DNA. Analysis of the transcripts by sucrose gradient sedimentation, polyacrylamide gel electrophoresis, and hybridization to separated strands and restriction endonuclease cleavages of the viral DNA demonstrated that the initiation of transcription is random and completely symmetric. Experimental data are discussed in terms of the function and regulation of RNA polymerase III during Ad2 infection and the components necessary to effect selective transcription in reconstructed systems. (38 refs.)

- 78-1170 Comparison of tRNA-Methylases from Normal and Tumor Tissues. I. Methylase Spectra in Kidney and Carcinoma RA.** (Rus) Deev, V. A. (Inst. Molecular Biology, Moscow, USSR); Venkstern, T. V.; Bayazitov, A. *Mol Biol (Mosk)* 11(5): 981-993; 1977.

The cause of the elevated methylase activity in tumor tissue was studied in albino rats bearing the transplanted carcinoma RA. Preparations of transfer RNA (tRNA) methylases isolated from the kidney and carcinoma tissue, and their activity and spectrum were assessed autoradiographically and electrophoretically. The total methylase activity in the tumor tissue was almost two times greater than that in kidney tissue, but the nuclease activity in the former was significantly higher than that in the latter. The increase in total tumor methylase activity was primarily due to elevation of the content of the component m<sup>3</sup>U. (22 refs.)

- 78-1171 Comparison of tRNA-Methylases from Normal and Tumor Tissues. II. Position Specificity**



ylases from Rat Kidney and Carcinoma RA. (Rus) V. A. (Inst. Molecular Biology, Moscow, USSR); T. V.; Bayev, A. A. *Mol Biol (Mosk)* 11(5): 994-997, 1977.

position specificity of the transfer RNA (tRNA) methylase from rat kidney and carcinoma RA tissue was assessed. tRNA<sup>Val</sup> was used as the substrate. Analysis of the products showed that both methylases had a similar position specificity; i.e., they methylated the same adenosine residue (A59) in the valine tRNA molecule. The m<sup>1</sup>A-methylase activity in the carcinoma was almost two times greater than in kidney tissue. (17 refs.)

172 **Changes in Bovine Lymphocyte DNA Methylation in Chronic Lymphocytic Leukemia.** (Rus) N. N. (Inst. Chemical Physics, Moscow, USSR); V. M.; Itkin, B. Z.; Vanyushin, B. F. *Biokhimiya* 16: 1691-1696; 1977.

Comparative analysis was made of the nucleotide composition and methylation level of lymphocyte DNA in healthy mice and cows with a histologically verified diagnosis of chronic lymphocytic leukemia. The DNA from the leukemic lymphocytes had a significantly decreased level of 5-methylcytosine (5-MC) (1.11%, compared to 1.35% in healthy controls). Since the DNA from leukemic and normal lymphocytes had a similar nucleotide composition (the amount of guanosine-cytosine pairs in both constituted 46.0% of the genome), as well as a similar distribution of trimidine blocks, it was suggested that the differences in 5-MC content are not due to changes in the DNA molecules, but rather to reduced methylation of the genome. Incubation of DNA preparations with the DNA methylase from *Escherichia coli* showed that the ratio of newly synthesized methyladenosine in the DNA from leukemic lymphocytes was on an average 1.7 times greater than that in the DNA from normal lymphocytes. Thus, the DNA's from these two types of lymphocyte differ in their acceptor capacity. (22 refs.)

173 **Stimulation of DNA Synthesis by Insulin in Organ Cultures of Benign Human Breast Tumors: Influence of Days in Culture (Meeting Abstract).** (Eng) C. W. (Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824); Patten, S. E.; Haviland, T. J.; McMahon, J. *Fed Proc* 37(3): 450; 1978. (no refs)

174 **Ethidium Bromide Binding to Transfer RNA: Transfer RNA as a Model System for Studying tRNA Interactions.** (Eng) Jones, C. R. (Dept. Biochem-

istry, Univ. Wisconsin, Madison, WI); Bolton, P. H.; Kearns, D. R. *Biochemistry* 17(4): 601-607; 1978.

The interaction of ethidium bromide (EB) with transfer RNA (tRNA) was examined using optical and <sup>1</sup>H nuclear magnetic resonance (<sup>1</sup>H NMR) methods. Optical measurements indicated that the strongest EB binding site is intercalative, with about three additional nonintercalative sites being occupied at high EB levels. The <sup>1</sup>H NMR data for mixed and pure species of tRNA indicated that none of the residues involved in the tertiary structure are adjacent to, or disrupted by, the strongly bound EB. The strong binding site in yeast tRNA-Phe and *Escherichia coli* tRNA-Val<sub>1</sub> is adjacent to the sixth base pair of the amino acid acceptor stem. Results for other class I tRNAs are consistent with the strong binding site being located in the amino acid acceptor stem, but some other binding sites cannot be ruled out on the basis of <sup>1</sup>H NMR alone. Yeast tRNA-Leu<sub>3</sub>, a class III tRNA, demonstrates spectral changes upon EB binding that are different from those of the class I tRNAs examined. The results for this class III tRNA are interpreted in terms of a unique EB binding site in the extra arm that stabilizes the base pairs of this stem. *E. coli* tRNA-fMet appears to have several binding sites of similar binding strength. These findings are consistent with the notion that the tertiary structure of tRNA restricts the binding of EB to a single site in the amino acid acceptor stem, and this site could be the same for all tRNA's. (52 refs)

78-1175 **Comparison of Polysomal Polyadenylated RNA from Embryonal Carcinoma and Committed Myogenic and Erythropoietic Cell Lines.** (Eng) Affara, N. A. (Institut Pasteur, Dept. Biologie Molculaire, 25, rue du Dr. Roux, 75015 Paris, France); Jacquet, M.; Jakob, H.; Jacob, F.; Gros, F. *Cell* 12(2): 509-520; 1977.

The polysomal poly(A)<sup>+</sup> messenger RNA (mRNA) base-sequence complexity in mouse embryonal carcinoma cells, myoblast cells, and Friend erythroleukemia cells was examined in mRNA-complementary DNA experiments. The cells expressed 7,700, 13,200, and 6,200 mRNA sequences, respectively, distributed in three frequency classes. A subset of 6,000 sequences was present on the polysomes of all three cell types. All embryonal carcinoma cell sequences were present on the myoblasts, but about 4,500 myoblast sequences, drawn primarily from a rare frequency class, were specific for the myoblasts. At least 6,000 Friend polysomal poly(A)<sup>+</sup> mRNA sequences were common to the embryonal carcinoma cells. An additional 1,500 sequences present in the embryonal carcinoma cells and apparently derived from a rare frequency class appeared to be absent in Friend cell polysomes. The sequence data suggest that commitment of embryonal carcinoma cells to erythroid or myogenic differentiation is not based simply on the selection of a subset of sequences already present in the polysomes. Rather, it appears to involve the expression of new gene sequences, in addition to a large popu-



lation of common mRNA's, and the quantitative modulation of certain shared sequences. (42 refs.)

- 78-1176 Studies of Human Histone Messenger RNA. II. The Resolution of Fractions Containing Individual Human Histone Messenger RNA Species.** (Eng) Borun, T. W. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104); Ajiro, K.; Zweidler, A.; Dolby, T. W.; Stephens, R. E. *J Biol Chem* 252(1): 173-180; 1977.

Polyribosomal 4S to 18S RNA from S-phase HeLa S-3 cells was fractionated by chromatography on oligo(dT)-cellulose and resolved into multiple discrete components by continuous elution preparation electrophoresis. The human histone messenger RNA (mRNA) species associated with various polyadenylated [poly(A(+))] and nonpolyadenylated [poly(A(-))] components of the RNA fractions were determined by translation in vitro in a Krebs II ascites cell-free system, followed by resolution of the histones synthesized in vitro on polyacrylamide gels containing Triton X-100. The results indicate that poly(A(-)) 4S to 18S RNA polyribosomes contains: (1) large quantities of discrete 7.4S and 8S RNA that are not functional histone mRNA; (2) a discrete 8.6S RNA that contains the templates of human histone H4; (3) 9.2S to 10.7S RNA that contains mixtures of incompletely resolved histone H2B, H2A, and H3 mRNA; (4) discrete 12S and 13S RNA fractions that contain templates of human histone III polypeptides. The mRNA templates of histone variants H3.2 and H3.3 have a slightly lower electrophoretic mobility than H3.1 mRNA, and H2A.2 mRNA has a slightly lower electrophoretic mobility than H2A.1 mRNA. Appreciable quantities of H3.2, H3.3, and H2A.2 mRNA are bound to oligo(dT)-cellulose in 0.5 M KCL. These results indicate that mRNA species of the same histone class differ slightly in primary structure and are consistent with the hypothesis that some histone mRNA species contain short tracts of poly(A). (15 refs.)

- 78-1177 Comparison of mRNA Binding by Met-t-RNA<sup>f</sup> Binding Protein and mRNA associated Proteins.** (Eng) Barrieux, A. (Div. Endocrinology, Dept. Medicine, Univ. California at San Diego Sch. Medicine, La Jolla, CA 92093); Rosenfeld, M. G. *J Biol Chem* 252(1): 392-398; 1977.

Phosphocellulose and DEAE-cellulose chromatography and isoelectric focusing demonstrated that one of the heterogeneous activities which bound messenger RNA (mRNA) in the 0.5 M KCL eluate of rabbit polyribosomes copurified to apparent homogeneity with the guanosine triphosphate (GTP)-dependent methionyl-transfer RNA-f (Met-tRNA<sup>f</sup>) binding protein. Analysis by sodium dodecyl sulfate-polyacrylamide gel electrophoresis following iodination revealed putative subunits with mol wts of 51,000 and 39,000 daltons. Specificity

of mRNA binding by this protein was suggested, since ability of poly(A)-rich mRNA to compete for binding. <sup>3</sup>H-poly(A)-rich mRNA was 10-100 times greater than that of most natural or synthetic RNA's tested, except for hybrid poly(G)-poly(C), which was almost as effective, poly(G), which was more effective. The mRNA binding activity exhibited complete GTP independence and no apparent divalent cation requirement. Guanosine diphosphate (GDP) inhibited Met-tRNA<sup>f</sup> binding, but neither GDP, guanosine monophosphate, nor 7-methylguanosine monophosphate inhibited mRNA binding by this protein. Similar data were obtained with respect to the ability of natural or synthetic RNA's to compete for binding of 11-(A)-rich mRNA by proteins associated with purified rat reticulocyte polyribosomal in mRNA-protein particles. Although poly(A) was an ineffective competitor, poly(G) was more effective than even mRNA in competing for protein-dependent binding. No significant binding of Met-tRNA<sup>f</sup> to mRNA-protein particles was detected. Polyacrylamide gel electrophoresis following reduction of mRNA-protein particles revealed apparent comigration of a major protein subunit of the GTP-dependent Met-tRNA<sup>f</sup> binding protein, but no protein comparable to the 39,000-dalton subunit. (61 refs.)

- 78-1178 Protein Phosphorylation in Normal and Neoplastic Development. Cyclic AMP-dependent Protein Kinase Activity in Urethane-induced Pulmonary Tumors.** (Eng) Malkinson, A. M. (Dight Inst. Human Genetics, Univ. Minnesota, Minneapolis, MN 55455); Gundersen, T. J.; McSwigan, C. E. *Biochem J* 168(2): 319-321; 1978.

Lung tissue samples were taken from tumor and unirradiated areas from A/Umc and A/St mice previously injected with 1 mg urethane and from healthy controls, and the cyclic AMP-dependent protein kinase specific activities of cytosolic fractions were determined. Both basal and cyclic AMP-stimulated activities in tumors were two-fold higher than those of normal lung; this elevated activity appeared to be tumor-specific. (22 refs.)

- 78-1179 Reduced Rates of Proteolysis in Transformed Cells.** (Eng) Gunn, J. M. (Dept. Biochemistry and Biophysics, Texas A & M Univ., College Station, TX 77843); Clark, M. G.; Knowles, S. E.; Hopgood, M. F.; Lard, F. J. *Nature* 266(5597): 58-60; 1977.

Protein degradation rates were investigated in nongrowing rat liver hepatocytes and chemically transformed R6 H35 hepatoma to see if a reduction in intracellular proteolysis could account for the uncontrolled growth of transformed cells. Fourteen percent of the normal hepatocytes broke down during a 4-hr incubation in salt medium, a rate that was greater than that for transformed cells. Lower rates for



toma cells were also noted in Eagle's minimal essential medium (MEM). Addition of insulin at the beginning of degradation inhibited intracellular protein breakdown in both cell types, but it was effective at lower concentrations in the transformed cell ( $10^{-12}$  M vs  $10^{-10}$  M). The difference in degradation appeared to reflect a changed genotype that was independent of cell growth rates. When the experiment was repeated with BALB/c 3T3 fibroblasts and transformed fibroblasts transformed by simian virus 40, the results were similar. It is concluded that transformed cells have a higher receptor affinity for insulin and this largely determines the lower protein degradation rates. (15 refs.)

**180 Role of Cell Surface Carbohydrates and Proteins in Cell Behavior: Studies on the Biochemical Reversion of an N-Acetylglucosamine-deficient Fibroblast Mutant.** (Eng) Pouyssegur, J. (Laboratoire des Membranes CNRS, INSA. Bat 406, 69621 Villeurbanne, France); Willingham, M.; Pastan, I. *Proc Natl Acad Sci USA* 74: 243-247; 1977.

Investigation of the biochemical properties of AD6, a mutant derived from 3T3 BALB/c cells in which the biosynthesis of complex carbohydrates and glycoproteins is impaired because of a block in the acetylation of glucosamine-6-phosphate, was studied. AD6 is characterized by low adhesion to a substratum, round shape, increase in surface microvilli, increase in agglutinability by concanavalin A (Con A), and loss of directional motility, properties associated with transformed cells. However, the mutant has normal growth properties and anchorage-dependence, it does not form tumors. Feeding N-acetylglucosamine-6-phosphate to this mutant (the next generation after the acetylation block) restored synthesis of the carbohydrate portion of the glycoprotein to normal, and the cell-surface glycoproteins became normally exposed. This biochemical reversion was accompanied by a complete restoration of the altered biological properties. The results suggest that one or more of the cell-surface glycoproteins plays a direct role in cellular adhesion. The fact that a defined alteration of the cell surface induced properties often encountered in transformed cells, without affecting cell division, suggests that these alterations of properties are not sufficient to account for the loss of growth regulation. (25 refs.)

**181 Changes in Nuclear Actin Levels with Change in Growth State of C3H 10T1/2 Cells and the Effect of Response in Malignantly Transformed Cells.** (Eng) Ram, J. S. (Dept. Experimental Therapeutics and Grace Cancer Drug Center, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY 14263); Libby, P. R.; Courgeon, W. M. *Cancer Res* 37(11): 4104-4111; 1977.

A protein that appeared identical to skeletal muscle actin was detected in highly purified nuclei from C3H/10T1/2 clone 8 mouse embryo fibroblast (10T1/2) cells and from transformed cell lines (10T1/2) derived from the parent line by carcinogen treatment (20-methylcholanthrene, N-acetoxyacetylaminofluorene, and N-methyl-N'-nitro-N-nitrosoguanidine). With discontinuous sodium dodecyl sulfate-polyacrylamide gel electrophoresis, nuclear actin levels were increased about twofold (5.5%-9.0% of residual nuclear protein) when logarithmic growth phase 10T1/2 cells [labeling index (LI), 53%] were grown to post-confluence inhibition of cell division (LI, 2%). In contrast, the T10T1/2 lines grew to saturation densities fivefold higher than those of the parent 10T1/2 cells, but the LI remained high (33%-42%) and nuclear actin concentrations remained low (5.6%-6.4%). The electrophoretic profile of residual nuclear proteins from logarithmic phase 10T1/2 cells was indistinguishable from logarithmic or plateau phase transformed cells. The actin content of whole 10T1/2 cells or whole T10T1/2 cells was about 5.5% regardless of growth state. When T10T1/2 cells were exposed to 1% dialyzed serum and isoleucine-free medium for 4 days, the LI decreased to 5%, but the nuclear actin concentration remained at about 5.5%. In contrast, 10T1/2 cells arrested in late G<sub>1</sub> phase by isoleucine deprivation (LI, 1.7%) exhibited high nuclear actin levels. Thus, the concentrations in these purified nuclei appear to be related to the commitment of cells to proliferate, rather than to the proliferation rate itself. A second protein, identified as the A<sub>1</sub> protein of HnRNP particles (mol wt, 32,000), was the only other protein to change in concentration on these gels. Its concentration appears to be directly related to cell proliferation rate. (40 refs.)

**78-1182 Mechanism of the Decrease in the Major Cell Surface Protein of Chick Embryo Fibroblasts after Transformation.** (Eng) Olden, K. (Lab. Molecular Biology, NCI, Bethesda, MD 20014); Yamada, K. M. *Cell* 11(4): 957-969; 1977.

Regulation of the major cell-surface glycoprotein of cultured chick embryo fibroblasts (CSP, a large external transformation-sensitive protein) was investigated by examining sizes of intra- and extracellular CSP pools, rates of CSP biosynthesis, transit times to the cell surface, and degradation rates before and after transformation by Rous sarcoma virus (RSV). CSP synthesis, measured by immunoprecipitation after pulse-labeling with <sup>14</sup>C-leucine, was decreased three to six times after transformation by the Bryan higher-titer, Schmidt-Ruppin, and temperature-sensitive ts68 and T5 strains of RSV. Steady-state quantities of CSP in intracellular pools were also decreased four to five times after transformation. The rate at which newly synthesized CSP was processed and exported to the cell surface was similar before and after transformation. Degradation and release of CSP from the cells



were measured after labeling for 24 hr. The half-life of CSP on normal cells was 36 hr, but it decreased to 16-26 hr after transformation. The amount of intact CSP released into the culture medium was decreased three fold after transformation; these amounts, however, represent losses of 20% and 40% of the total CSP synthesized by normal and transformed cells, respectively. The results indicate that the major mechanism for the decrease in CSP after transformation is reduction in its biosynthesis, although increased degradation and loss from the cell surface also contribute significantly. These changes account for the observed five- to sixfold decrease in cell-associated CSP after transformation of chick embryo fibroblasts. The decreased biosynthesis appears to be due to decreased transcription of CSP messenger RNA after transformation. (33 refs.)

- 78-1883 **Globin Synthesis in Mouse Erythroleukemia Cells In Vitro: A Switch in  $\beta$  Chains Due to Inducing Agent.** (Eng) Alter, B. P. (Div. Hematology and Oncology, Children's Hosp. Medical Center, 300 Longwood Ave., Boston, MA 02115); Goff, S. C. *Blood* 50(5): 867-876; 1977.

Dimethyl sulfoxide, butyric acid and hemin stimulated globin synthesis in strain 745 Friend leukemia cells from DBA/2 mice. Although balanced globin synthesis was noted with all agents, the first two compounds stimulated  $\beta$  major chains more than  $\beta$  minor, while hemin stimulated  $\beta$  minor chains more than  $\beta$  major. The morphology of the cells depended on the stimulating agent used. This system can be used to study regulation of globin-chain switching. (28 refs.)

- 78-1184 **Collagenolytic Activity of Rabbit V<sub>2</sub>-Carcinoma Growing at Multiple Sites.** (Eng) Biswas, C. (Developmental Biology Lab., Massachusetts General Hosp., Boston, MA, 02115); Moran, W. P.; Bloch, K. J.; Gross, J. *Biochem Biophys Res Commun* 80(1): 33-38; 1978.

The influence of site of tumor growth on the collagenolytic activity of serially transferred V<sub>2</sub> rabbit carcinoma was investigated. Extracts from im tumors in 19 rabbits were assayed after activation with trypsin, and only 2 had activatable enzyme. In contrast, all the extracts from seven sc tumors possessed collagenolytic activity after activation with trypsin. Histologically, there was no difference between the im and sc initiated tumors. In five rabbits, im and sc tumors were initiated simultaneously and assayed for enzyme activity. Trypsin-activatable collagenase activity was found in tumors from both sites in all animals. This result could be due to a stimulatory effect of the sc tumor on the im tumor. The inability to extract collagenase from the im tumors in the absence of sc tumors could be due to nonsynthesis of the enzyme or to its existence as an irreversible enzyme-inhibitor complex. (10 refs)

- 78-1885 **Chromatin Phospholipids in Normal and Chronic Lymphocytic Leukemia Lymphocytes.** (Eng) Manzoli, F. A. (Istituto di Istologia ed Embriologia Generale, Via Belmeloro, 8, 40126 Bologna, Italy); Maraldi, M.; Cocco, L.; Capitani, S.; Facchini, A. *Cancer Res* 37: 843-849; 1977.

The phospholipid content and the composition of the different chromatin fractions obtained from chronic lymphocytic leukemia (CLL) lymphocytes, which represent particular modifications of nonhistone chromosomal proteins (NH) and histone fractions, were investigated. B cells constituted approx 92% of the total lymphocytes, T cells < 8%. The phospholipids, sphingomyelin, phosphatidylcholine, phosphatidylethanolamine were present in normal CLL B lymphocytes. The av ratio for the three 50:10:40, respectively, in normal B lymphocytes 20:40:40, respectively, in CLL lymphocytes. T compared to normal B cells, sphingomyelin was reduced to about 40% but phosphatidylcholine increased fourfold in the CLL cells. It is suggested that the altered phospholipid composition bound to NH could influence chromatin assembly and gene transcription. (41 refs.)

- 78-1186 **Phospholipids of Plasma Membranes Isolated from Rat Ascites Hepatomas and from Normal Rat Liver.** (Eng) Koizumi, K. (Dept. Clinical Biochemistry, Faculty Pharmacy, Meijo Univ., Nagoya 468, Japan); Tamiya-Koizumi, K.; Fujii, T.; Kojima, K. *Cell Struct Funct* 2(2): 145-153; 1977.

Phospholipid class composition and plasmalogen content and its location within the cells were analyzed in AH 62, AH 130FN, AH 602, AH 7974, and AH 7974F rat ascites hepatomas and in liver samples from normal Moriyama rats to examine the relationship between lipid abnormalities and biological properties of malignant cell plasma membranes (PM). In hepatoma and normal liver, PM phospholipids tended to have a higher percentage of sphingomyelin (Sph) and a lower percentage of phosphatidylcholine (PC) in whole cell lipids. Hepatomas contained higher percentages of Sph, phosphatidylethanolamine, and phosphatidylserine (PS) and a lower percentage of PC than normal liver. Hepatoma and normal liver had similar phosphatidylcholine percentages. The island-forming hepatoma PM had a higher PS percentage of total phospholipid phosphorus than the free-cell-type PM. The phospholipid composition of the ganglioside fraction from the hepatoma was similar to the corresponding fractions from normal liver, except for generally lower lysophospholipid percentages in the hepatoma fractions and higher Sph and PS percentages in the hepatoma. The percentage of choline phospholipid was significantly lower in hepatoma cells than in normal liver; the reverse was true for ethanolamine phospholipid. These differences were marked in the PM fraction than the whole cell; they were



ved in the microsomal fraction, and there was a reverse  
nity in the mitochondrial fraction. Hepatoma cells gen-  
contained higher plasmalogen-type phospholipids than  
al cells. The island-forming hepatoma had remarkably  
r total fatty aldehyde and plasmalogen contents than  
ree-cell type. Mitochondrial and microsomal fractions  
hepatoma cells also contained higher fatty aldehyde  
the corresponding fractions from normal liver. Intracel-  
plasmalogen was detected in the PM and cytoplasmic  
les of all hepatomas. (25 refs.)

187 **NADPH-dependent Lipid Peroxidation in  
Mitochondria from Livers of Young and Old  
and from Rat Hepatoma D30.** (Eng) Player, T. J. (Dept.  
chemistry, Univ. Birmingham, Post Office Box 363, Bir-  
ham B15 2TT, England); Mills, D. J.; Horton, A. A.  
em Soc Trans 5(5): 1506-1598; 1977.

es of NADPH-dependent lipid peroxidation, measured  
ne formation of thiobarbituric acid-reactive material,  
ed a substantial increase in the peroxidation rate in liver  
chondria from old rats (26 mo) compared with mature  
(6 mo). Almost no peroxidation occurred in mito-  
dria from the rat hepatoma D30. The possible role of  
radicals and peroxides in rendering mitochondrial mem-  
es vulnerable to carcinogenesis is discussed. (10 refs.)

188 **Effect of Lipids on the Expression of Cell  
Transformation.** (Eng) Corwin, L. M. (Dept.  
obiology and Cancer Res. Center, Boston Univ. Sch.  
icine, Boston, MA 02118); Humphrey, L. P.; Shloss, J.  
Cell Res 108(2): 341-347; 1977.

effect of lipids on BALB/c 3T3 clone A31 and K3T3  
was investigated. In studies with K3T3 cells, the addi-  
of 10 µg/ml of linoleic acid to delipidized fetal calf serum  
produced spindle cells with extrusions typical of fetal  
serum (FCS)-grown K3T3 cells. Vitamin E (2.5  
ml) added with the acid counteracted this effect  
resulted in cells with the appearance of untrans-  
ed A31 cells. Addition of 10 µg/ml cholesterol  
ntuated the effect of linoleic acid. In examining  
adherence of these cells to the substratum, lino-  
leic acid, cholesterol and vitamin E added to AES  
ted in a transformation of the cells to resemble K3T3  
grown in FCS. When FCS-grown cells underwent one  
age in AES, a return to FCS produced a small cell size  
al of the transformed phenotype. However, when these  
were maintained in AES for five or more passages, their  
eased size was maintained even when returned to FCS  
ia. Continual passage in FCS prevented the return to the  
ler size. When K3T3 cells were grown in AES, they  
me sensitive to dextran sulfate, a characteristic found in  
nal cells. K3T3 cells grown in AES for five passages had

a higher saturation density when transferred to FCS, but this  
was still below that of cells grown continually in FCS. After  
several passages in FCS, AES-grown cells developed an  
intermediate saturation density in both sera. These  
results indicate that the phenotypic expression of cell  
transformation can be altered by changing the lipid  
composition of the medium. (19 refs.)

78-1189 **The Development of Thyroid Neoplasia in Old  
Age in the Amazon Molly, *Poecilia formosa*.**  
(Eng) Woodhead, A. D. (Biology Dept., Brookhaven Natl.  
Lab., Upton, NY, 11973); Setlow, R. B.; Hart, R. W. *Exp  
Gerontol* 12(5/6): 193-200; 1977.

The development of thyroid neoplasia in senile Amazon mol-  
lies (*Poecilia formosa*) was investigated and compared to that  
seen in a closely related species of laboratory guppies [*Le-  
bistes reticulatus* (Peters)]. Thyroid enlargement was noted  
in a few fish at 18 mo of age; in senile fish, the incidence  
reached 100%. The spontaneous growth occupied most of the  
pharyngeal region. Three zones of tissue were recognized: a  
center region with inactive follicles, a peripheral area domi-  
nated by microfollicles, and an outermost area with many  
afollicular epithelial cells. The growth was invasive, and it  
destroyed both bone and muscle. There was a great deal of  
similarity between the *P. formosa* and *L. reticulatus* neo-  
plasms, suggesting similar development. Massive thyroid  
growths were induced in young mollies by inoculating them  
with cells containing damaged DNA, and the induced lesions  
were compared with the spontaneous ones of older fish. There  
was a striking similarity between the two groups, with the  
induced neoplasms having a regular appearance. It is suggest-  
ed that the spontaneous lesions arise from the inability of the  
aging thyroid to respond to thyrotropic hormone and that  
differences between spontaneous and induced neoplasms re-  
flect a different hormonal status. (9 refs)

78-1190 **Prostaglandins and Breast Cancer.** (Eng) Ben-  
nett, A. (Dept. Surgery, King's Coll. Hosp.  
Medical Sch., London SE5 8RX, England); McDonald, A.  
M.; Stamford, I. F.; Charlier, E. M.; Simpson, J. S.; Zebro,  
T. *Lancet* 2(8039): 624-626; 1977.

Prostaglandin content was studied in 66 mammary car-  
cinomas from women aged 36 to 87 yr, 16 benign neoplasms  
from women aged 16 to 63 yr, and in macroscopically normal  
tissue from 23 mastectomy specimens. Total, basal, and syn-  
thesized amounts of prostaglandinlike activity were signifi-  
cantly higher in extracts of malignant tumors than those of  
benign tumors or normal tissue. Tumors from patients with  
bone metastases produced more prostaglandins than those  
from patients with no evidence of spread. Total and basal  
levels were higher in invasive tumors. There was no correla-  
tion between total, basal, or synthesized amounts of prosta-



glandinlike material from the malignant tumors with tumor size, histological type, border of growth, grade of malignancy, sinus histiocytosis in lymph nodes, fibrous tissue production, cellular infiltration around the tumor, or predominant cell type. It is suggested that prostaglandins might be involved in local tumor spread. (6 refs.)

- 78-1191 Estriol Production Rates and Breast Cancer.** (Eng) Pratt, J. H. (Dept. Medicine, Univ. Indiana, Indianapolis, IN); Longcope, C. *J Clin Endocrinol Metab* 46(1): 44-47; 1978.

The endogenous concentrations, metabolic clearance rates, and blood production rates of estrone, estradiol, and estriol were measured in seven women with breast cancer and five normal postmenopausal women. Labeled estrone, estradiol, and estriol were infused into the women, and blood samples were obtained from the contralateral arm. There were no significant differences between the respective measurements for each group. These findings do not support the argument that physiological amounts of estriol are protective against breast cancer development in women. (16 refs)

- 78-1192 Human Breast Cancer: Androgen Action Mediated by Estrogen Receptor.** (Eng) Zava, D. T. (Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284); McGuire, W. L. *Science* 199(4330): 787-788; 1978.

MCF-7 human breast cancer cells were incubated with physiological ( $10^{-8}$  M) and pharmacological ( $10^{-6}$ ) concentrations of dihydrotestosterone (DHT), and the effects on estrogen, androgen, progesterone, and glucocorticoid receptors were examined. At  $10^{-8}$  M DHT, the cytoplasmic androgen receptor was translocated to the nucleus, and a significant portion of the estrogen receptor was depleted; other receptors were not affected. Testosterone and androstenediol were equally effective at inducing the depletion and translocation of the cytoplasmic estrogen receptors; progesterone and hydrocortisone had no effect. When intact cells were exposed to  $10^{-8}$  M DHT, progesterone receptor levels remained unaltered; in cells exposed to  $10^{-6}$  M DHT, these levels were significantly stimulated. Thus, the androgen-translocated nuclear estrogen receptor must be active at specific gene acceptor sites. It is suggested that the failure of androgens to induce tumor regression in certain breast cancer patients may be related to the paradoxical estrogenic effects of pharmacological concentrations of androgens. (9 refs)

- 78-1193 Correlative Study of the Morphology and  $C_{19}$ -Steroid Metabolism of Benign and Cancerous Human Prostatic Tissue.** (Eng) Morfin, R. F. (Laboratoire

de Biochimie, Faculte de Medecine de Brest, Brest, France); Leav, I.; Charles, J. F.; Cavazos, L. F.; Ofner, P.; Floch, H. *Cancer* 39(4): 1517-1534; 1977.

Perineal punch biopsy specimens of human prostate with benign hyperplasia (BPH), poorly or well-differentiated adenocarcinoma, and transitional cell carcinoma were incubated with  $^3$ H-testosterone and  $^3$ H-5 $\alpha$ -dihydrotestosterone. The incubations were carried out using a single tissue: radio substrate ratio and time point. The resulting radio steroid patterns were related to the histologic and ultrastructural features of these tissues. Well-differentiated neoplasms had ultrastructural characteristics closely resembling hyperplastic epithelia. In BPH and in well-differentiated carcinomas, the  $C_{19}$ -steroids were mainly metabolized by the 17 $\beta$ -hydroxysteroid pathway. In contrast, cells of poorly differentiated adenocarcinomas and transitional cell carcinomas lacked cytoplasmic organelles responsible for secretion; formation of 5 $\alpha$ -reduced 17 $\beta$ -hydroxysteroids was increased in these carcinomas but conversion to 17-oxosteroid radiometabolites remained unchanged or was greatly decreased. These results indicate that loss of prostatic differentiation is accompanied by a trend from reductive toward oxidative radiotestosterone metabolism. Even in NADPH-supplemented preparations of poorly differentiated tumors there was diminished transformation to dihydrotestosterone, the key intracellular hormone in expression of prostatic androgenic activity. These findings may explain why poorly differentiated prostatic neoplasms are frequently unresponsive to antiandrogenic therapy. (21 refs.)

- 78-1194 Effects of Thyroxine, Insulin and Cholesterol on the Amount of Cyclic Adenosine Monophosphate (cAMP) in Normal Cells and in Cells Infected with Oncornavirus.** (Rus) Bershtein, L. M. (Lab. Endocrinology, Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR); Lindeberg, T. Ia.; Gaber, V. K.; Kostetskiy, T. V.; Kuznetsov, O. K.; Dil'man, V. M. *Tsitologiya* 19(10): 1006-1010; 1977.

The intracellular concentrations of cyclic AMP in normal cells and chicken fibroblasts infected with Rous sarcoma virus were measured. Addition of 2  $\mu$ g/ml thyroxine increased the levels of cyclic AMP in both types of cells; insulin (2  $\mu$ g/ml) decreased the concentration, and cholesterol (5  $\mu$ g/ml) had no effect. The possible influence of hormones on cholesterol accumulation in cells and adenylate cyclase activity in cell membranes is discussed. (21 refs.)

- 78-1195 Cyclic AMP, the Microtubule-Microfilament System, and Cancer.** (Eng) Puck, T. T. (Ele



evelt Inst. Cancer Res., Inc., 4200 E. Ninth Ave., Denver, CO 80262). *Proc Natl Acad Sci USA* 74(10): 4491-4495;

existence in normal fibroblasts of a cyclic AMP-dependent network of microtubules and microfilaments demonstrated. This network is connected with cell membrane elements on one end and nuclear structures on the other, and its disorganization leads to malignant transformation. In the presence of cyclic AMP derivative sufficient to promote the integrity of this network, formed Chinese hamster embryo fibroblasts exhibited (1) no growth in agar suspension, (2) an increase in  $\alpha$ - $^{14}$ C-aminobutyrate transport, and (3) the relative membrane of normal fibroblasts. The pulsating membrane responsible for membrane hyperactivity in the transformed state were shown to be associated with aggregated deposits near the membrane. Specific orientations of tubular and filamentous elements with respect to the nucleus were demonstrated. The hypothesis that the microtubular-microfilamentous structure conveys growth regulatory information from the cell membrane to the nucleus and that its disorganization can lead to malignancy has been extended to explain various cellular manifestations. (36

96 **Exit Transport of a Cyclic Nucleotide from Mouse L-Cells.** (Eng) Plagemann, P. G. (Dept. Biology, Medical Sch., Univ. Minnesota, Minneapolis, MN 55455); Erbe, J. *J Biol Chem* 252(6): 2010-2016; 1977.

release of 1,4,5,6,8-pentazaacenaphthylene, 3-amino-1,5-dihydro-5-methyl-1- $\beta$ -D-[5- $^{14}$ C]ribofuranosyl, a tricyclic, 7-purine nucleoside (TCN) from mouse L cells, was investigated. At a concentration of 30  $\mu$ M, TCN is rapidly taken up by the cells and converted to intracellular TCN phosphate (TCN-P), but it is not further metabolized. TCN-P is also excreted by the cells into the medium; the release is a saturable process against a concentration gradient, is inhibited by various inhibitors of energy production. Effectiveness of dinitrophenol, sodium azide, KCN, and acetate in preventing the release of TCN-P was related to their effectiveness in depleting the ATP pool of cultured cells. This implicates a role for active transport in the release of TCN-P. The transport system is highly temperature-dependent and is inhibited by papaverine, theophylline, Probenecid, phenethyl alcohol, and p-mercuribenzoate, but not by 500  $\mu$ M cyclic AMP, GMP, or adenosine. Significant amounts of AMP, ATP, GMP, or monophosphate, uridine diphosphate, and phosphorylcholine were not released under the experimental conditions, either in the presence or absence of TCN. Since TCN-P is not released from HEP-2 cells, the release may be confined to certain types of cells or animal species. (19 refs.)

78-1197 **Nonreiterated Sequence Transcripts in Two Rat Transplantable Hepatomas (Meeting Abstract).**

(Eng) Garrett, C. T. (George Washington Univ. Medical Center, Washington, DC, 20037); Gonzalez, F. J.; Kilner, J. *Fed Proc* 37(3): 749; 1978. (no refs)

78-1198 **Experimental Elimination and Recovery of Double Minute Chromosomes in Malignant Cell Populations.** (Eng) Levan, G. (Inst. Genetics, Univ. Lund, S-223 62 Sweden); Mandahl, N.; Bengtsson, B. O.; Levan, A. *Hereditas* 86(1): 75-90; 1977.

Environmental effects on the frequency of cells with double minute chromosomes (dms) were studied in the SEWA mouse ascites tumor. Under normal in vivo conditions, this tumor contained about 90% cells with one or more dms. Explantation in vitro decreased the dms-carrying cells to 5% of the population after 100 days. Following reimplantation in vivo, the original proportion of these cells was restored after 170 days. A mathematical model describing these changes as selective phenomena is presented. In the stock tumor, almost all minute chromosomes were C-band-negative. In the experimental populations, both in vivo and in vitro, minute chromosomes appeared that were C-band-positive. By other morphologic and functional criteria, they were shown to be small chromosomes and not dms. The fact that dms have been found only in malignant cells and the correlation established in these experiments between the presence of dms and in vivo environment lead to speculations concerning their function. One possibility is that they involve the amplification of gene material significant to tumor development. (17 refs.)

78-1199 **Studies on Force-Breeding and Social Density as They Relate to Mammary Tumor Formation in Mice (Meeting Abstract).** (Eng) Cooley-Matthews, B.

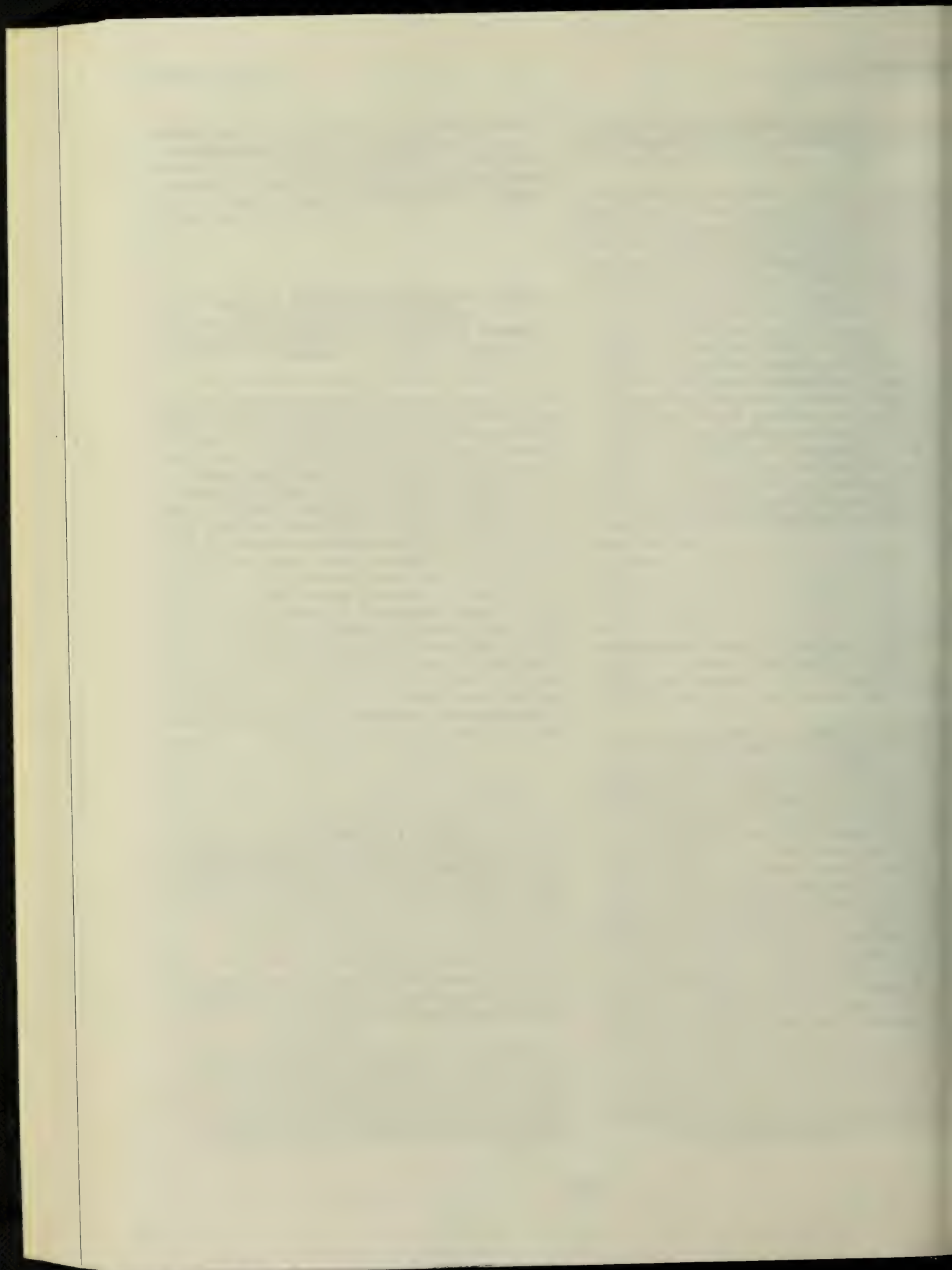
(Univ. Southern California, Los Angeles, CA 90007). *Diss Abstr Int B* 38(3): 1064; 1977. (no refs.)

78-1200 **General Theory on the Control of Cell Cycle.**

(Eng) Erhan, S. (2101 Chestnut St., Philadelphia, PA, 19103). *Med Hypotheses* 4(1): 58-77; 1978.

A model for control of the cell cycle based on the antagonistic effects of replication-triggering and mitosis inhibiting proteins is presented. With this model, neoplastic change would result from any agent that interferes with the formation of these receptor molecules or leads to the destruction of already existing membranes or membrane receptors. (119 refs)







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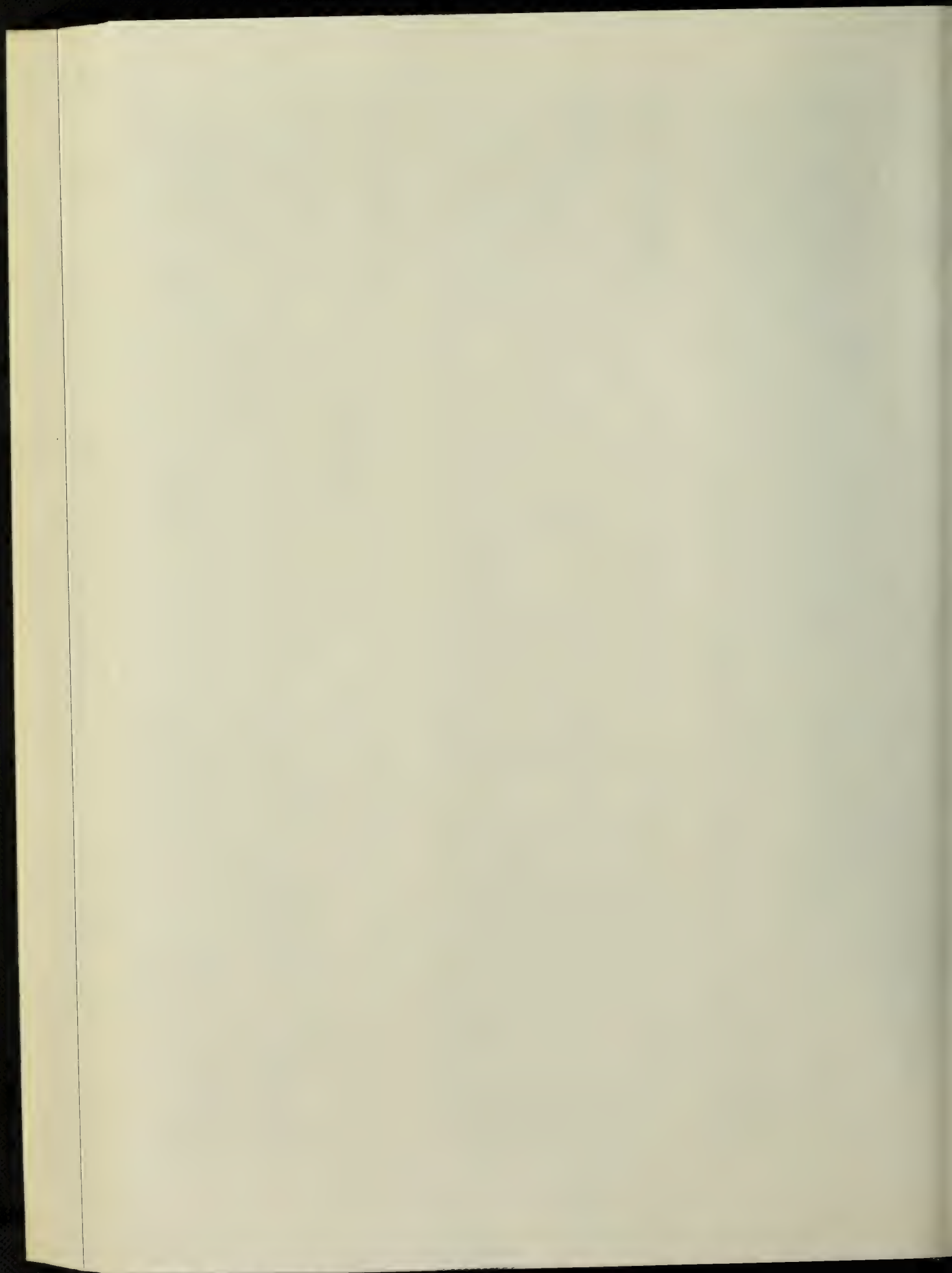


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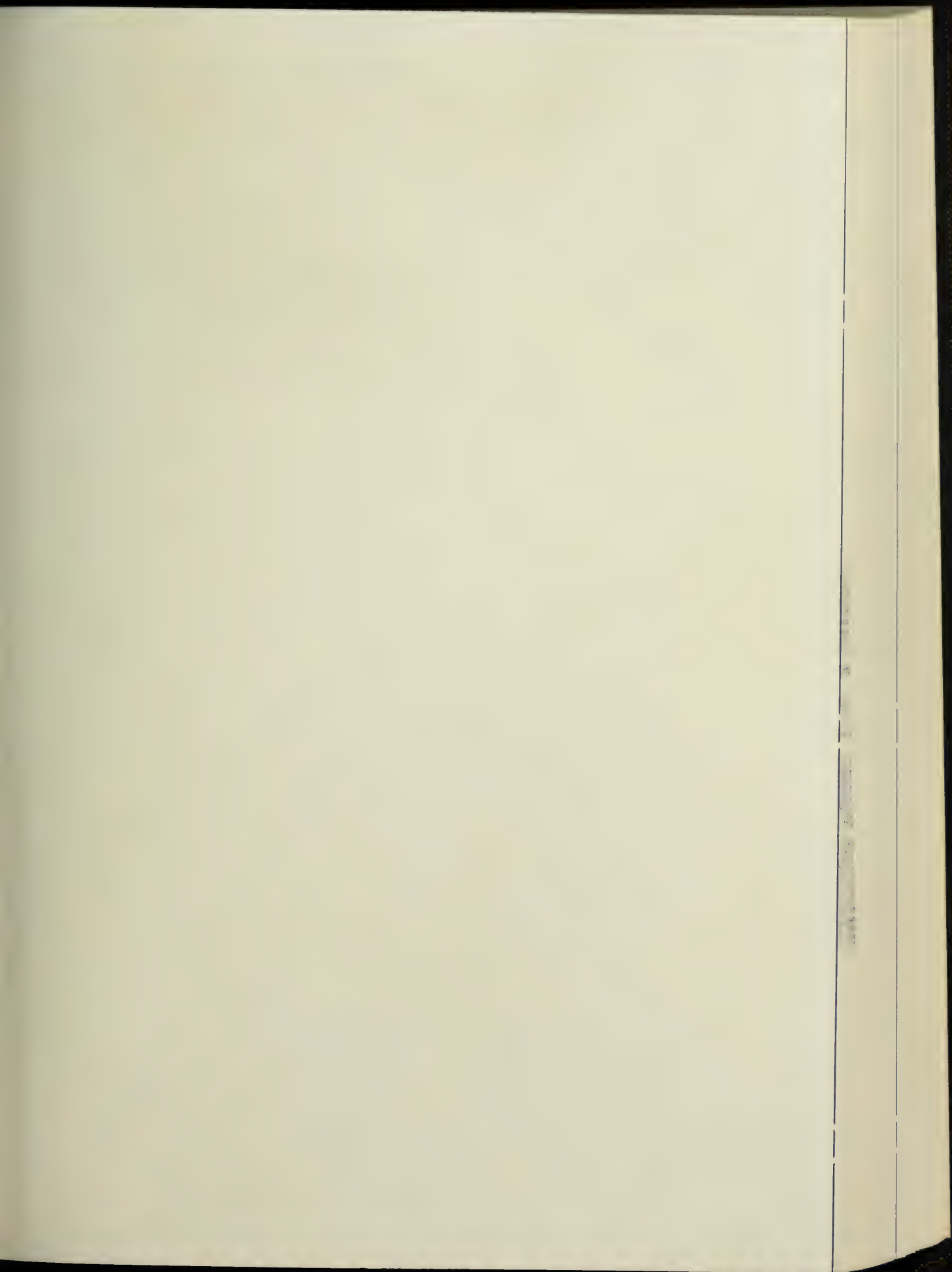
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# CARCINOGENESIS ABSTRACTS

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## **EDITOR**

**GEORGE P. STUDZINSKI, M.D., Ph.D.**  
COLLEGE OF MEDICINE AND DENTISTRY  
OF NEW JERSEY, NEWARK

## **ASSOCIATE EDITOR**

**JUSSI J. SAUKKONEN, M.D.**  
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PHILADELPHIA

## **NCI STAFF CONSULTANTS**

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**JOAN W. CHASE, M.S.**

*Literature Selected, Abstracted, and Indexed*  
*by*

*Information Services Department, Science Information Services Organization*

**BRUCE H. KLEINSTEIN, Ph.D., J.D., Assistant Director, Biomedical Projects**

**RUTHANN E. AUCHINLECK, Managing Editor**

**The Franklin Research Center**  
**The Benjamin Franklin Parkway, Philadelphia, Pennsylvania 19103**



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# CARCINOGENESIS ABSTRACTS

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### GENERAL INFORMATION

CARCINOGENESIS ABSTRACTS makes available abstracts, annotations or citations of significant carcinogenesis articles collected from the current major biomedical sources of world literature. This service is provided by the National Cancer Institute through a contract with the Franklin Research Center for preparation of the publication, under Contract No. NOI-CP-75885 with the National Cancer Institute, U.S. Department of Health, Education and Welfare. Published and distributed by the Franklin Institute Press<sup>SM</sup>.

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## ABBREVIATIONS

**JOURNAL** names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

**LANGUAGE** of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

**ABBREVIATIONS** used in abstracts:

<b>A</b>	angstrom(s)	<b>mOsm</b>	milliosmolar
<b>ACTH</b>	adrenocorticotrophic hormone	<b>max</b>	maximum
<b>ADP</b>	adenosine diphosphate	<b>mEq</b>	milliequivalent(s)
<b>AMP</b>	adenosine monophosphate	<b>min</b>	minute(s)
<b>ATP</b>	adenosine triphosphate	<b>ml</b>	milliliter(s)
<b>approx</b>	approximately	<b>μl</b>	microliter(s)
<b>av</b>	average	<b>mm</b>	millimeter(s)
<b>BCG</b>	bacillus Calmette-Guerin	<b>mo</b>	month(s)
<b>bid</b>	twice daily	<b>mol wt</b>	molecular weight
<b>C</b>	degree(s) centigrade	<b>N</b>	normal concentration
<b>cal</b>	calorie(s)	<b>NAD</b>	nicotinamide adenine dinucleotide
<b>kcal</b>	kilocalorie(s)	<b>NADH</b>	reduced nicotinamide adenine dinucleotide
<b>cc</b>	cubic centimeter(s)	<b>NADP</b>	nicotinamide adenine dinucleotidephosphate
<b>Ci</b>	curie(s)	<b>NADPH</b>	reduced nicotinamide adenine dinucleotidephosphate
<b>mCi</b>	millicurie(s)	<b>NCI</b>	National Cancer Institute
<b>μCi</b>	microcurie(s)	<b>NIH</b>	National Institutes of Health
<b>cm</b>	centimeter(s)	<b>PAS</b>	periodic acid-Schiff
<b>CNS</b>	central nervous system	<b>po</b>	orally
<b>cpm</b>	counts per minute	<b>ppb</b>	parts per billion
<b>DNA</b>	deoxyribonucleic acid	<b>ppm</b>	parts per million
<b>ED<sub>50</sub></b>	median effective dose	<b>qid</b>	four times daily
<b>EDTA</b>	ethylenediamine tetraacetic acid	<b>qod</b>	every other day
<b>g</b>	gram(s)	<b>QO<sub>2</sub></b>	oxygen quotient
<b>kg</b>	kilogram(s)	<b>R</b>	roentgen
<b>mg</b>	milligram(s)	<b>RBC</b>	red blood cells (erythrocytes)
<b>μg</b>	microgram(s)	<b>RNA</b>	ribonucleic acid
<b>Hb</b>	hemoglobin	<b>rpm</b>	revolutions per minute
<b>hr</b>	hour(s)	<b>sc</b>	subcutaneous
<b>ia</b>	intra-arterial	<b>sec</b>	second(s)
<b>id</b>	intra-dermal	<b>SGOT</b>	serum glutamic-oxaloacetic transaminase
<b>IgA</b>	Immunoglobulin A	<b>SGPT</b>	serum glutamic-pyruvic transaminase
<b>IgB</b>	Immunoglobulin B	<b>soln</b>	solution
<b>IgG</b>	Immunoglobulin G	<b>TCD</b>	tissue culture dose
<b>IgM</b>	Immunoglobulin M	<b>TCD<sub>50</sub></b>	median tissue culture dose
<b>ILS</b>	increased life span	<b>tid</b>	three times daily
<b>im</b>	intramuscular	<b>UV</b>	ultraviolet
<b>ip</b>	intraperitoneal	<b>WBC</b>	white blood cells (leukocytes)
<b>IU</b>	International Unit(s)	<b>wk</b>	week(s)
<b>iv</b>	intravenous	<b>wt</b>	weight
<b>Km</b>	Michaelis constant	<b>X</b>	times
<b>LD</b>	lethal dose	<b>yr</b>	year(s)
<b>LD<sub>50</sub></b>	median lethal dose		
<b>M</b>	molar		
<b>μM</b>	micromolar		



## REVIEW

- 78-1201 Interspecific Comparison of Ethyl Methanesulfonate-induced Mutation Rates in Relation to Genome Size.** (Eng) Schalet, A. P. (Dept. Radiation Genetics, Sylvius Labs., State Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands). *Mutat Res* 49(3): 313-340; 1978.

Experimental data from various systems used in a previous report that concluded that there is a relationship between ethyl methanesulfonate (EMS)-induced mutation rate and genome size, as has been suggested for radiation, are examined in detail. It is noted that 2/9 mutation rates cited came from seed treatments of higher plants, and they were not converted to the haploid-genome mutation rates necessary for a valid comparison with other test systems. The use of EMS-induced mutation rates from *Drosophila* and mouse postmeiotic male germ cells for comparisons with radiation-induced mutation rates from *Drosophila* and mouse spermatogonia is inappropriate. The method of using the actual initially applied concentration of EMS alone as a measurement of dose is criticized. However, when this method was used, no evidence was found for a relationship between EMS-induced haploid-genome mutation rate and genome size in organisms ranging from *Escherichia coli* to *Hordeum vulgare*, which differ in DNA content by a factor  $> 1,000$ . X-ray equivalent values differed by more than two orders of magnitude from one test system to another and by one order of magnitude for different male germ cells of *Drosophila*. A previous analysis of the available data for radiation-induced mutation rates found no relationship between mutation rate and genome size. It is considered that the failure to find a relation between EMS mutation rate and genome size from the type of analysis suggested in the previous report has no bearing on the utility of the recombination concept. (66 refs)

- 78-1202 Metabolic Activation of Chlorinated Ethylenes: Dependence of Mutagenic Effect on Electrophilic Reactivity of the Metabolically Formed Epoxides.** (Eng) Henschler, D. (Institut für Toxikologie, Universität Würzburg, Versbacher Landstrasse 9, D-8700 Würzburg, W. Germany); Bonse, G. *Arch Toxicol (Berl)* 39(1/2): 7-12; 1977.

Investigations of the chemical reactivity, biotransformation, and toxicity of the chloroethylenes are reviewed. In chlorinated ethylenes, the chlorine substitution exerts, by its electron-withdrawal effect, a stabilization of the molecule that increases with the number of chlorine residues. Epoxides are short-lived metabolic intermediates that rearrange to give two possible products: acylchlorides (as with tetra-, tri-, and 1,1-dichloroethylenes) or aldehydes (1,2-cis- and 1,2-trans-dichloroethylenes and vinyl chloride). The aldehydes subsequently undergo reduction and oxidation to alcohols and

acids, respectively. The chlorinated ethylenes were tested for mutagenic potential in a modified Ames system, and three members of the group were active: vinyl chloride, vinylidene chloride, and trichloroethylene. The molecular feature common to the active molecules is an unsymmetric chlorine substitution, but in the inactive compounds there is a symmetric distribution of the chlorine residues. It is hypothesized that the increased electrophilicity caused by the asymmetrical chlorine substitution offers an enhanced chance for alkylating reactions of the epoxides, which overpower the deactivation mechanisms of conjugation, rearrangement, and hydrolysis. The three mutagenic chloroethylenes have also produced carcinogenic effects in animals. (14 refs)

- 78-1203 Does Sarcoma Occur in Man after Intramuscular Iron?** (Eng) Fielding, J. (Hematology Dept., St. Mary's Hosp., London W9 3 RL, England). *Scand J Haematol* (Suppl.32): 100-104; 1977.

Analysis of the literature indicates that several factors influence sarcoma induction at the site of high-dose iron-carbohydrate complex injection in animals. These include (1) species specificity, (tumors have been induced in rats, mice, and hamsters but not in guinea pigs or dogs); (2) dose response (a threshold dose may be defined and tumor yields increase with dose); (3) the amount of residual iron at the injection site; and (4) the latent period relative to life-span in the species, which has led to an estimate of a 15- to 20-yr latent period in man. Nine malignancies in man allegedly related to iron-complex injection have been described during the period 1960-1977. A review of the information available on these cases suggests that in only one case are the data sufficiently strong to support the probability of iron-dextran-induced sarcoma in man. The occurrence of malignancy of any type in the buttock is not common, but it is not very rare either. Since this is a favored site for iron injections of all kinds, it is important that the occurrence of these tumors in relation to all injectables should be recorded. The occurrence of a single case of sarcoma at the site of iron injections, during a 22-yr period in which millions of injections were given, is not sufficient to establish a causal relationship. (18 refs)

- 78-1204 Metabolic Activation of Diethylstilbestrol and Aminostilbene-Derivatives.** (Eng) Neumann, H. G. (Institut für Pharmakologie und Toxikologie, Universität Würzburg, Versbacher Landstrasse 9, D-8700 Würzburg, W. Germany); Metzler, M.; Topner, W. *Arch Toxicol (Berl)* 39(1/2): 21-30; 1977.



Diethylstilbestrol (DES) and trans-4-dimethylaminostilbene are metabolically activated, and several of their metabolites react with cellular macromolecules. Epoxidation of the stilbene double bond is a major pathway in the metabolism of stilbenes. The rates of the epoxide inactivation reactions, which compete for possible reactions with cellular nucleophiles, probably differ considerably, and this could contribute to the differential toxicity of these compounds. However, available data on the chemical and mutagenic activity of the epoxides of DES and cis- and trans-4-dimethylaminostilbene are conflicting and do not permit conclusions to be drawn linking this particular metabolic pathway to detrimental effects. Other data suggest that the  $\omega$ -hydroxylation of dienes, formed through the oxidation of DES, represents another activating pathway, but the toxic potential of the reactive metabolites has not been established. Nitroso-derivatives have also been considered as the ultimate carcinogens, but studies have indicated that although nitroso-derivatives are present in the liver, they are inactivated efficiently through a reaction with thiol groups. The question remains as to which metabolites escape inactivation and are delivered into the circulation and which are activated in extrahepatic tissues. (35 refs)

- 78-1205 Noncontraceptive Estrogens and Abnormalities of Endometrial Proliferation.** (Eng) Weiss, N. S. (Dept. Epidemiology, SC-36, Univ. Washington, Fred Hutchinson Cancer Res.Center, Seattle, WA, 98195). *Ann Intern Med* 88(3): 410-412; 1978.

A review of data linking the use of noncontraceptive estrogen preparations with hyperplasia and adenocarcinoma of the endometrium in menopausal women is presented. The risk ratio appears to be greater for hyperplastic and less-aggressive malignant lesions and smaller for tumors with higher stages and grades. This inverse relationship between estrogen use and degree of malignancy is probably due to early or liberal diagnoses of endometrial cancer among estrogen users, but it could indicate that estrogens promote less-aggressive tumors. The present data suggest that the excess risk can be lessened by the use of lower doses and shorter durations of total use. It appears that the current increased incidence of endometrial cancer in the US will not be followed by an increase in mortality from the disease. (20 refs)

- 78-1206 Kepone--Hazard Evaluation.** (Eng) Epstein, S. S. (Sch. Public Health, Box 6998, Univ. Illinois Medical Center, Chicago, IL). *Sci Total Environ* 9(1): 1-62; 1978.

A lengthy review is given of kepone, a persistent chlorinated hydrocarbon pesticide no longer manufactured (as of April 1977) in the US. Kepone is acutely toxic, and it induces cumulative and delayed toxicity, neurotoxicity, and repro-

ductive impairment in birds, rodents, and humans. It is hepatocarcinogenic in rodents, and the experimental data have a high degree of presumptive human relevance. Its effects on highly exposed employees of one manufacturing plant (1974-1975) are reported. (52 refs)

- 78-1207 Report and Final Resolutions of an International Workshop on the Toxicology of Benzene.** (Fre) Truhaut, R. (France). *Arch Mal Prof* 38(10/11): 967-978; 1977.

Experimental data show that benzene causes bone marrow depression and chromosome aberrations. Epidemiological data indicate that there is an increased incidence of leukemia in workers following long-term inhalation of benzene vapors (no refs)

- 78-1208 Genetic Toxicology of Benzene, Toluene, Xylenes and Phenols.** (Eng) Dean, B. J. (Sittingbourne Res. Center, Shell Res. Ltd., Sittingbourne, Kent ME9 8AG, Great Britain). *Mutat Res* 47(2): 75-97; 1978.

The mutagenicity of several industrial solvents, benzene (BZ), toluene, o-, m-, and p-xylene, and 15 phenol compounds, is reviewed, and reference is made to their biotransformation and carcinogenicity. Since the discovery that phenols were mitotic spindle poisons, the subject has been studied extensively in plants but not in microorganisms and mammals. Similarly, the BZ/leukemia association has stimulated extensive investigations of the clastogenic properties of the solvent but not its ability to induce gene or point mutations. Prolonged exposure to high BZ concentrations results in myelotoxicity, but the differences in individual susceptibility to this hazard remain unexplained. Structural and numerical chromosome alterations occur in animals given large doses of BZ. Evidence for chromosome damage in symptom-free workers exposed to BZ is less convincing. Extensive chromosome alterations have been found in patients suffering from BZ-induced myelotoxicity, but the precise relationship between the hemopathies and chromosome damage is uncertain. Almost all patients with BZ leukemia were exposed extensively to other chemicals, although BZ was common to them all. Other environmental factors are likely to be involved, and a co-leukemic role for BZ would explain the failure to reproduce BZ leukemia in animals. The carcinogenicity data for the review compounds are limited. Skin-painting studies suggest that BZ is not carcinogenic by this route. A single application of phenol to mouse skin stimulated cell mitosis, and repeated application of a 20% soln resulted in a high incidence of papillomas. Phenol, o-, m-, and p-cresol, toluene, and xylene can act as tumor promoters. The skin carcinogenicity of these compounds appears to be associated with their irritancy and their subsequent formation of skin hyperplasia. (90 refs)



78-1209 **Chrysotile Asbestos: Effects of Human Exposure (Letter to Editor).** (Eng) Rohl, A. N. (Environmental Sciences Lab., Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029); Langer, A. M.; Jlikoff, I. J. *Science* 198(4323): 1202; 1977.

Contrary to a statement in a previous letter, exposure to chrysotile asbestos has been linked with pulmonary fibrosis, asbestosis, thickening and calcification of the pleura, and respiratory, mesothelial, and gastrointestinal malignant tumors. People with the longest exposure to the highest concentrations are those most at risk. Unnecessary exposure to chrysotile asbestos should be avoided. (6 refs)

78-1210 **Detection and Prevention of Health Hazards in the Rubber Industry.** (Eng) Parkes, H. G. (CIMA Health Res. Unit, Birmingham, England). *Plastics and Rubber: Processing* 2(4): 149-152; 1977.

Experience gained in the detection and elimination of occupational bladder cancer as a major industrial hazard affecting the rubber industry emphasizes the need for more effective techniques for detecting and preventing future health hazards. Although the connection between bladder tumors and the use of aromatic amines in the dyestuffs industry was first suggested in 1895, the first step to eliminate exposure was not taken in England until 1949, when the manufacture and commercial use of  $\beta$ -naphthylamine were abandoned. (In the US, use continued to 1972). In addition to closing plants manufacturing chemicals (benzidine,  $\alpha$ -naphthylamine) implicated in bladder cancer, screening programs were established for those considered to be at risk. More than 100 cases of pre-symptomatic stage bladder cancer have been detected in rubber workers exposed before 1950. Proposals for protection against future industrial health hazards must include a comprehensive screening program that will allow for the toxicity screening of all new and existing industrial materials, regular monitoring of the industrial environment, and routine medical supervision and epidemiological surveillance of employees. Careful documentation of occupational exposures is needed to detect long-term industrial cancer hazards. (12 refs)

78-1211 **Acrolein.** (Eng) Izard, C. (Res. Dept., Dir. Etud. Equip., 53 Quai d'Orsay, Serv. Exploit. Ind. b. Allumettes (SEITA), F 75 340 Paris Cedex 07, France); Hermann, C. *Mutat Res* 47(2): 115-138; 1978.

The biological activity of acrolein (AL), a substance that occurs in industrial fumes, tobacco smoke, and automotive exhaust, is reviewed. AL is highly reactive, and it affects the nucleus and locomotory apparatus of living cells. It is extremely irritating to the respiratory and ocular mucosae, and

it is toxic to animals, plants, and unicellular organisms. At the cellular level, it has cytotoxic, cilia-depressing effects. AL is a byproduct of the in vitro degradation of two antitumoral agents, cyclophosphamide and isophosphamide. In the presence of hepatic microsomal preparations, its patterns of formation from either agent are similar. Therefore, AL could play a role in the antitumor action of these drugs. However, in given circumstances, AL might also act as a premutagen and so produce glycidal (a compound that is carcinogenic on mouse skin) through epoxidation in vivo. AL might also have precarcinogenic activity through a similar mechanism. AL binds especially easily to nucleic acids, injuring nuclei and perturbing mitoses. It is hypothesized that the effects of AL are located in DNA or in enzymes intervening in nucleic acid synthesis. Thus, in vivo, AL might act as an anticarcinogen or, on the contrary, as a precarcinogen and a precursor of glycidal. (98 refs)

78-1212 **Carcinogenic Effect of Hydrazines.** (Hun) Baló, J. (I. Korbontani Intezet, Semmelweis Orvostudományi Egyetem, Budapest, Hungary). *Orv Hetil* 118(50): 3011-3013; 1977.

Hydrazines were found to induce tumors of the intestines, lungs, and kidneys in rats, mice, and golden hamsters. The findings call for studies on the possible carcinogenic effect of isoniazid in tuberculous patients treated with this drug. (40 refs.)

78-1213 **Caffeine.** (Eng) Timson, J. (Dept. Medical Genetics, Medical Sch. Univ. Manchester, Manchester, M13 9PL, England). *Mutat Res* 47(1): 1-52; 1977.

The biological, physiological, mutagenic, and teratogenic effects of caffeine are reviewed. Although caffeine is mutagenic in lower animals, there is no evidence that it is a mutagen in mammals, probably because it is rapidly metabolized. At high doses, however, it appears to have some teratogenic activity. (390 refs)

78-1214 **Contraindicated Drugs in the Pregnant Woman.** (Fre) Delavest, P. (Hopital Lariboisiere, Service de gynecologie-obstetrique, 2, rue Ambroise-Pare, 75010 Paris, France). *Rev Prat* 28(11): 791-792; 1978.

The potential teratogenic or mutagenic effects of drugs, hormones, or other medicines that might be prescribed during pregnancy are reviewed. Except for the antifolic agents and androgens, no teratogenic agent comparable to thalidomide has been discovered. However, many drugs may have weak teratogenic effects. Toxic or oncogenic effects may appear



later in the life of the exposed fetus; mutagenic effects may result in impaired fertility. (5 refs)

- 78-1215 Sex-Specific Carcinogens, with Special Reference to Saccharin. (Letter to Editor).** (Eng) Wigle, D. T. (Cancer Section, Bureau Epidemiology, Lab. Centre for Disease Control, Health and Welfare Canada, Ottawa, Ontario K1A 0L2, Canada). *Lancet* 1(8058): 279; 1978.

Criticism of the sex specificity of saccharin carcinogenesis in man, based on the argument that no nonhormonal carcinogen in man is sex specific, is stated to be invalid. Animal studies have revealed at least 22 sex-specific carcinogens that cause tumors such as hepatomas, lymphomas, sarcomas, and mixed tumors. (no refs)

- 78-1216 Mutagenic and Teratogenic Effects of Cigarette Smoke. A Summary of Experimental and Clinical Observations.** (Ger) Marczinski-Verheugt, E. (Jacob-van-Lennep-Strasse 28, Venlo, Holland); Doerfler, W. *Munch Med Wochenschr* 120(10): 327-330; 1978.

Cigarette smoke condensate has a mutagenic effect on *Salmonella typhimurium* in the Ames test. Epidemiological observations show significantly increased perinatal mortality and a frequency of malformations (meningomyelocele, anencephaly, urogenital and limb malformations) among the children of fathers who are heavy smokers. (31 refs)

- 78-1217 The Effects of Smoking on the Lungs.** (Eng) Woolcock, A. J. (Dept. Medicine, Univ. Sydney, New South Wales 2006, Australia); Berend, N. *Aust NZ J Med* 7(6): 649-662; 1977.

The effects of smoking on lung structure and function are reviewed, as is the evidence relating smoking to lung disease. The major respiratory problems caused by smoking are lung cancer, chronic bronchitis, chronic bronchiolitis, and emphysema. It is believed that the causative factors of these conditions are found in the tar component of the tobacco. (171 refs)

- 78-1218 New Evidence Concerning Smoking and Health.** (Eng) Gray, N. (Anti-Cancer Council Victoria, 90 Jolimont St., East Melbourne, Victoria 3002, Australia); Donovan, J. W. *Med J Aust* 2(16): 543-544; 1977.

A previous article in which it was argued that lung cancer and smoking are unrelated and that a variety of occupational

and environmental agents cause the disease is criticized. Although occupational exposure does cause some lung cancers among blue collar workers, most of them are smokers, and the occupational exposure acts as a synergistic agent. (9 refs.)

- 78-1219 Statistical Appraisal of the Association of Smoking and Chewing Habits to Oral and Pharyngeal Cancers.** (Eng) Jayant, K. (Epidemiology Div., Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay-400 012, India). *Indian J Cancer* 14(4): 293-299; 1977.

Studies of oral cancer in India are reviewed, and the causal significance of the chewing and smoking of tobacco is examined. The data show that chewing tobacco quid is causally associated with oral cancer and bidi smoking is causally associated with pharyngeal cancer. Tobacco appears to have weak carcinogenic properties, and it needs a co- or synergistic agent to manifest its potential. Betel nut chewing also appears to have some carcinogenic potential, and evidence suggests that betel nut extract accelerates tobacco carcinogenesis. Bidi smoke contains both benzantracene and benzo(a)pyrene, at concentrations higher than those in cigarette smoke. Furthermore, a majority of oral, oropharyngeal, and hypopharyngeal cancers can be accounted for by the chewing and smoking of tobacco, actions that interact synergistically. (27 refs)

- 78-1220 Cultural and Behavioral Aspects of Risk Factors: Society's Obligation.** (Eng) Wynder, E. L. (American Health Foundation, 1370 Ave. of the Americas New York, NY, 10019). *J Environ Pathol Toxicol* 1(2): 11-18; 1977.

Individual and societal actions that could be taken to reduce cancer risk are considered. The reduction of tobacco smoking should be approached from three areas: (1) education, (2) smoke cessation programs, and (3) development of a less harmful cigarette. Individual preventive action with regard to nutrition can be effected by reducing the intake of whole milk, butter, and meat, especially beef. In terms of managerial preventive medicine, the reduction of fat in all dairy products and in beef is recommended. More research is needed to determine the extent to which, if any, vitamin or mineral deficiencies relate to specific cancers. Heavy alcohol consumption has been established as a risk factor for cancer of the mouth, larynx, and esophagus, primarily in smokers. This promotional effect of alcohol is probably related to nutritional deficiencies, a dietary condition commonly associated with excessive alcohol intake. Occupational exposures are estimated to be related to <5% of total cancer incidence among men and <1% among women. Nevertheless, every occupational cancer death should be and possibly could be avoided. Agents in the workplace that may increase cancer risk should be eliminated or reduced to an acceptable minimum. (11 refs)



8-1221 **Epidemiological Bases for Primary Prevention of Cancer.** (Ger) Berndt, H. (Klinik für Innere Medizin, Bezirkskrankenhaus, PSF 480, DDR-20 Neubrandenburg, E. Germany). *Dtsch Gesundheitsw* 32(52): 2449-453; 1977.

Epidemiological data are presented on the major human cancers and on the environmental and endogenous factors that may facilitate or prevent them. An unbalanced diet, abuse of tobacco and alcohol usage, sexual promiscuity, and excessive sunbathing are among the factors facilitating the development of certain cancers in humans. (35 refs)

8-1222 **Environmental Carcinogens in Modern Society.** (Rus) Higginson, J. (International Cancer Research Agency, Lyons, France). *Vopr Onkol* 23(12): 8-16; 1977.

In this review, current data on the role of various environmental factors in the etiology of cancer are summarized. Almost 80% of all human cancers are caused by exogenous factors, which include not only occupational hazards and environmental pollutants, but also smoking, alcohol consumption, and dietary habits. Voluntary changes in a person's lifestyle might significantly reduce his risk of cancer. (26 refs)

8-1223 **Environmental Factors in Chemical Carcinogenesis.** (Rus) Shabad, L. M. (Dept. Carcinogenic Agents, Cancer Res. Center, Moscow, USSR). *Gig Sa-hig* (11): 46-50; 1977.

The results of numerous extensive studies on the detection and quantitative assessment of various environmental carcinogens are reviewed. Data on cancer morbidity in various migrant groups are indicative of the role of environmental factors in the incidence and, thus, the possible prevention of cancer. (no refs)

8-1224 **Environmental Factors and the Development of Disease and Injury in the Alimentary Tract.** (Eng) Schedl, H. P. (Dept. Medicine, Univ. Iowa Coll. Medicine, Iowa City, IA, 52242). *Environ Health Perspect* 20: 39-44; 1977.

Interactions between the alimentary tract and various environmental agents are reviewed. N-Nitroso compounds, which are among the most important environmental carcinogens, are present in certain foods and they can be formed in the gastrointestinal tract. Microflora may activate a potential carcinogen or detoxify it. Diet may also influence carcinogenesis. Environmental factors play a key role in the genesis of cancer of the esophagus, stomach, colon, and rectum. (48 refs)

78-1225 **Chemical Carcinogenesis in the Gastrointestinal Tract.** (Ger) Hoensch, H. (Abteilung Innere Medizin I, Medizinische Universitätsklinik, Otfried-Müller-Strasse 10, 7400 Tübingen, W. Germany); Fleischmann, R. *Dtsch Med Wochenschr* 102(42): 1516-1520; 1977.

Several carcinogens, benzo(a)pyrene, biphenyls, nitrosamines, cycasine, and aflatoxin B<sub>1</sub>, were found in the human diet. In addition, *Clostridium parapatrificum* may be able to metabolize bile acids to carcinogenic substances. Diet, bacterial flora, and the bile acid content of the colon appear to influence the development of colonic tumors in man. (51 refs.)

78-1226 **Comparative Analysis of Contamination of Food Products with Polycyclic Aromatic Hydrocarbons in USSR and East Germany.** (Rus) Fritz, V. (Central Inst. Nutrition, Berlin, E. Germany); Engst, R.; Shabad, L. M.; Dikun, P. P.; Khesina, A. Ya. *Vopr Pitan* (6): 20-23; 1977.

The association between carcinogenic additives in food and the incidence of cancer of stomach is discussed. Environmental carcinogens account for more than three-fourths of the digestive system tumors. Although a complete ban on all food products containing carcinogenic additives is unlikely, the results of extensive research should constitute the scientific basis for the appropriate legislation. (45 refs)

78-1227 **HSE Publish First Comprehensive Statistics on Health and Safety at Work.** (Eng) Anonymous (No affiliation given). *Mining Eng* 137(197): 171; 1977.

A report by the British Health and Safety Executive documents the number of work-related accidents and occupational diseases for the years 1971-1975. Of deaths from occupational diseases, the largest numbers were from pneumoconiosis (577), mesothelioma (61), and asbestosis (50). (2 refs.)

78-1228 **Significance of Various Enzymes in the Control of Mutagenic and Carcinogenic Polycyclic Hydrocarbons.** (Ger) Oesch, F. (Abteilung für Molekularpharmakologie, Pharmakologisches Institut der Universität, Obere Zahlbacherstrasse 67, D-6500 Mainz, W. Germany). *Hautarzt* 28(11): 563-573; 1977.

The effect of homogeneous rat liver epoxide hydratase (EH) on electrophilic, ie, mutagenically active, metabolites of benzo(a)pyrene (BP) and other hydrocarbons is reviewed. EH was found to be a specific broad-spectrum enzyme for epoxides. There was a dose-dependent increase in the number of



reverted *Salmonella typhimurium* TA 1537 colonies in the presence of BP, a metabolic activator (mouse liver homogenate and NADPH, for monooxidase), and EH. The mutagenically reactive metabolites synthesized by control or phenobarbital-induced cytochrome P-450-dependent monooxygenases (almost all monofunctional epoxides) were good substrates for EH, but the dihydrodiol epoxides biosynthesized by 3-methylcholanthrene-induced cytochrome P-448-dependent monooxygenases were poor substrates. Many substances proved to be inducers of EH and also the monooxygenase responsible for epoxide formation. Since the induction of these enzymes can be dissociated, a selective induction of EH should be possible. The constitutive activities of EH are inherited in a codominant way, but the inducibility is under polygenetic control. The EH isolated from skin was similar to hepatic EH. Therefore, the considerable difference in susceptibility to polycyclic hydrocarbon-induced carcinogenesis between the skin and liver cannot be explained by the presence or absence of this enzyme, nor by differently behaving EH's. Compared with the skin, however, the liver has a significantly higher concentration of either the same EH or of a functionally similar enzyme. The EH activity of mouse liver is considerably lower than that of human EH, making the mouse a poor model for toxicological and carcinogenesis studies. (29 refs.)

- 78-1229 Dual Role of Glucuronyl- and Sulfotransferases Converting Xenobiotics into Reactive or Biologically Inactive and Easily Excretable Compounds.** (Eng) Bock, K. W. (Abteilung Biochemische Pharmakologie, Institut für Pharmakologie und Toxikologie, Universität Göttingen, Robert-Koch-Strasse 40, D-3400 Göttingen, W. Germany). *Arch Toxicol (Berl)* 39(1/2): 77-85; 1977.

The role of glucuronyl- and sulfotransferases in activating and inactivating xenobiotics is reviewed. These enzymes inactivate a wide variety of hazardous compounds, such as phenols and dihydrodiols, generated during the metabolism of polycyclic hydrocarbons. Glucuronide conjugation, for example, may reduce the formation of mutagenic intermediates of benzo(a)pyrene metabolism. This regulatory control of conjugation may explain the varied susceptibility of individuals to toxic agents. Uridine diphosphate-glucuronyltransferase is markedly activated by membrane perturbants in vitro and in vivo; eg, liver injury by carbon tetrachloride. Sulfotransferases, which are located in the cytoplasm, compete with the glucuronyltransferases for the same substrates. Sulfate esters and glucuronides of certain N-hydroxyarylamines (N-hydroxy-N-acetylaminofluorene, N-hydroxyphenacetin) are more reactive than the parent compound and bind covalently to cell constituents. Of the two conjugates, the sulfate ester is more reactive and therefore more toxic in the liver. The glucuronide may be important in the kidney and bladder, where it is highly concentrated. Glucuronides have been implicated in bladder cancer after  $\beta$ -naphthylamine poisoning; 1-hydroxy-2-

naphthylamine glucuronide causes bladder cancer when instilled directly into the urinary bladder. (31 refs)

- 78-1230 The Effect of Dose on Cancer Latency Period.** (Eng) Guess, H. A. (Natl. Inst. Environmental Health Sciences Res., Triangle Park, NC, 27709); Hoel, D. G. *J Environ Pathol Toxicol* 1(2): 279-286; 1977.

A mathematical analysis was applied to the results of other investigators that had led to the conclusion that at very low carcinogen doses, tumors would take so long to develop that life would end before they appeared. The proper analysis of latent period (time-to-tumor) data requires that the distribution of the latent period about its mean value be considered explicitly. Correct assessment of risks requires that the probability of developing a tumor before dying of something else be estimated directly. The apparent increase in tumor development time is nothing more than a manifestation of the mathematical fact that decreasing the incidence necessarily increases the latent period. No physical increase in tumor growth time need be postulated to explain the observations. Existing methods of low-dose risk extrapolation implicitly account for the increase in latent period statistics insofar as they account for the decrease in tumor incidence. (7 refs)

- 78-1231 Bayesian Analysis of a Dose-Response Experiment with Serial Sacrifices.** (Eng) Bratcher, T. L. (Univ. Southwestern Louisiana, Lafayette, LA, 70504). *Environ Pathol Toxicol* 1(2): 287-292; 1977.

A mathematical analysis was applied to carcinogenesis studies in which sacrifices were performed throughout the experiment. Estimates of the risk probability for each dose level and sacrifice time were found using the sample likelihood at the posterior density. The dose-response relationship was investigated with these estimates as the response. A Bayesian multiple comparisons technique was introduced to test if the dose is effective and to check the appropriateness of the time-to-incidence model. (8 refs)

- 78-1232 The Importance of Non-Linear (Dose Dependent) Pharmacokinetics in Hazard Assessment.** (Eng) Watanabe, P. G. (Health and Environmental Res. Toxicology Lab., Dow Chemical Co., Midland, MI 48640); Young, J. D.; Gehring, P. J. *Journal of Environmental Pathology and Toxicology* 1(2): 147-159; 1977.

The importance of dose-dependent or nonlinear pharmacokinetics in interpreting animal toxicity data at high dose level for subsequent assessment of the hazard of exposure to humans is illustrated by two examples, 1,4-dioxane and vinyl chloride. The biotransformation, excretion, and protein binding



of many chemicals are capacity-limited processes, and the probability of encountering saturable processes in animal toxicity tests is high. Toxicity at high doses may be due to saturated detoxification or excretion mechanisms that, when fully operative at lower doses, do not result in the same toxic response. Knowledge of the pharmacokinetics of a chemical, therefore, is essential in evaluating animal toxicity tests. Pharmacokinetic data can also be used to assist in dose selection for chronic toxicity studies. In both cases, maximum information is obtained from a well-defined dose-response relationship. Massive doses that result in nonlinear pharmacokinetics could be avoided unless they approximate human exposure levels. (20 refs)

78-1233 **Estimation of Low-Dose Risk of Carcinogens by the Median-Effect Equation of the Mass-Action Law (Meeting Abstract).** (Eng) Chou, T. C. (Sloan-Kettering Inst. Cancer Res., New York, NY, 10021). *Proc Am Assoc Cancer Res* 19: 162; 1978. (2 refs)

78-1234 **Considerations in Chronic Toxicity Testing: The Chemical, the Dose, the Design.** (Eng) Munro, I. C. (Bureau Chemical Safety, Food Directorate, Health Protection Branch, Tunney's Pasture, Ottawa, Canada, KIA OL 2). *J Environ Pathol Toxicol* 1(2): 183-197; 1977.

Three areas involved in the planning of chronic toxicity tests, chemical purity, dose selection, and experimental design, are reviewed. Special attention must be given to potential impurities that may be responsible wholly or in part for the production of toxic effects. Potential impurities have been identified in saccharin and food colors. Prior to initiating chronic toxicity studies, the purity of the starting materials used in the manufacture of the test chemical should be assessed carefully, the manufacturing procedure should be reviewed to identify actions that could produce impurities, and the stability of the test chemical during storage and in the diet or dosing vehicle should be determined. Before the selection of doses for carcinogen bioassays, the pharmacodynamic and, to the extent possible, metabolic behavior of the test compound should be examined to preclude the development of undesirable effects, apart from carcinogenesis, during bioassay. Whether or not bigenerational exposure is required to evaluate the carcinogenicity of the test substance will depend on the use pattern and pharmacokinetic and metabolic behavior of the mother and fetus. (23 refs)

78-1235 **Significance of In Vitro Tests of Chemicals for Carcinogenicity.** (Ger) Schramm, T. (Zentralinstitut für Krebsforschung, Bereich Chemische Kanzerogenese, Lindenberger Weg 80, DDR-1115 Berlin, E. Ger-

many); Teichmann, B.; Butschak, G. *Arch Geschwulstforsch* 47(6): 567-580; 1977.

Although the results of in vitro carcinogenicity tests of compounds have not yet been correlated completely with in vivo animal studies and human epidemiologic data, the tests are valuable for screening suspicious substances prior to long-term animal tests. (54 refs.)

78-1236 **Some Genetic Considerations for the Design of Better Mammalian Assay Systems for the Detection of Chemical Mutagens and Carcinogens.** (Eng) Wolff, G. L. (Dept. Health, Education and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR, 72079). *J Environ Pathol Toxicol* 1(2): 79-90; 1977.

Manipulation of the genetic constitution of laboratory test animals should help to develop more sensitive, relevant, and economical toxicologic assay systems for the generation of dose-response data at environmental exposure levels. Dominant visible mutations that enhance tumor formation can be incorporated in laboratory mouse populations of any desired genetic structure. Thus, two different levels of inherent susceptibility to tumor formation can be incorporated and visually identified in the same test population. Possibilities inherent in genetic manipulation can be illustrated with the dominant yellow mutations at the agouti locus on chromosome 2 in the house mouse, which produces a yellow coat and enhanced spontaneous and induced tumor formation. The genetic structure of a laboratory animal population can also be manipulated to generate F-1 hybrids, hybrid crosses, or minimally inbred stocks from the same gene pool. The suitability of these genetic structures to any particular case depends on the purpose for which the assay data will be used. Obtaining data for estimating the relative risks of particular chemicals to exposed human populations requires a population of test animals that mimics as closely as possible the wide variety of metabolic and physiological responses in the human population. (27 refs)

78-1237 **Strength and Weaknesses of Microbial Test Results for Predicting Human Response.** (Eng) de Serres, F. J. (Natl. Inst. Environmental Health Sciences, Triangle Park, NC, 27709). *J Environ Pathol Toxicol* 1(2): 43-48; 1977.

Short-term tests for mutagenicity in which various microbial strains have been combined with microsomal fractions derived from mammalian liver make it possible to screen large numbers of untested chemicals in the environment. The most widely used system is the Salmonella assay, which provides information on the induction of point mutations by measuring the reversion of various histidine-requiring strains. As part of a battery of tests that would include other microor-



ganisms to detect effects on the induction of point mutations, DNA repair, and mitotic recombinations and gene conversion, a screen can be developed that would be much more comprehensive than the Salmonella assay in isolation. However, even with the inclusion of these microbial assays, information important for humans is still lacking; ie, the induction of chromosome aberrations resulting in rearrangements of abnormal numbers of chromosomes or the induction of gene mutation by interstitial deletion. Test results from such screening programs are best used to identify environmental chemicals with mutagenic potential and to determine priorities for further testing of active chemicals. Informed risk evaluation requires both quantitative and qualitative data that can only be obtained from tests on higher organisms. The most promising use of the short-term test is quality control, not only with regard to formulated products but also with regard to the technical grade chemicals used as product constituents. (8 refs)

- 78-1238 Relationships Between Laboratory and Human Studies.** (Eng) Clayson, D. B. (Eppley Inst. Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NB, 68105). *J Environ Pathol Toxicol* 1(2): 31-40; 1977.

Problems in extrapolating the results of chemical carcinogenesis experiments on animals to humans are considered from the viewpoints of experimental techniques for establishing chemicals as carcinogens and the effect of modifying factors. Extrapolation from the effects of high doses of carcinogens in experimental animals to low doses in humans presents problems that are beyond the reach of present epidemiological and experimental methodology. It seems more reasonable to attempt a risk-benefit assessment on practical and observable issues than to invoke complex statistical arguments about the likely effect of low doses of carcinogens in humans. The processes of tumor formation and their modification are so numerous and complex that it is possible, in correlating a high dose in an experimental animal to a low dose in humans, that a qualitatively based pragmatic guess is better than a pseudoscientific, but mathematically sound, extrapolation. (28 refs)

- 78-1239 Modifying Factors in Chemical Carcinogenesis: Preliminary Classification.** (Rus) Bogovsky, P. A. (Inst. Experimental and Clinical Medicine, Tallin, USSR). *Vestn Akad Med Nauk SSSR* (10): 47-54; 1977.

A preliminary classification of modifying factors (MF) of chemical carcinogenesis is reported. MF can be divided into anticarcinogenic factors (ACMF: factors that inhibit carcinogenesis) and cocarcinogenic factors (CCMF: factors that enhance this process). CCMF include solvents, surface-active compounds, and agents that increase the solubility and resorption of benzo(a)pyrene. ACMF include adsorbents and

solvents that decrease the accumulation of carcinogens. The MF can be further subdivided into exogenous (food) and endogenous (age, sex, hormonal balance, metabolism) factors. (71 refs.)

- 78-1240 Evolution of the Concept of Chemical Carcinogenesis.** (Rus) Shabad, L. M. (Cancer Res. Center, Moscow, USSR). *Vestn Akad Med Nauk SSSR* (10): 11-14; 1977.

Various aspects of chemical carcinogenesis are discussed with special attention to the role of endogenous carcinogens and the host-mediated effects of exogenous carcinogens. (no refs)

- 78-1241 Established Principles and Unresolved Problems in Carcinogenesis.** (Eng) Berenblum, I. (Weizman Inst. Science, Rehovot, Israel). *J Natl Cancer Inst* 60(4): 723-726; 1978.

The general theory of carcinogenesis suggests that transformation takes place in two steps: the initiating phase and the promoting phase. Initially, there is an irreversible change in the genome of a cell by chemical, physical, virological, or accidental means. However, some findings contradict this mechanism of action. These include the following: strain, species, and organ differences in response to specific forms of carcinogenic action; carcinogenesis by hormone imbalance; carcinogenesis by sc implantation of plastic or metal films; and the transformation efficiency in vivo and in vitro. It is suggested that work on these latter phenomena will result in a method of tumor induction that will resolve the existing anomalies. (47 refs)

- 78-1242 Environment and the Skin.** (Eng) Suskind, R. F. (Inst. Environmental Health, Univ. Cincinnati Medical Center, Cincinnati, OH, 45267). *Environ Health Perspect* 20: 27-37; 1977.

Interactions between the environment and the skin that can result in pathology are outlined, as are the adaptive mechanisms in the skin. Keratoses, basal cell carcinomas, squamous cell carcinomas, keratoacanthomas, and, probably, melanomas are associated with solar radiation. Polycyclic aromatic hydrocarbons, combustion products of carbonaceous materials, inorganic arsenic compounds, ionizing radiation, and trauma also cause skin cancer. (42 refs)

- 78-1243 Does Ultraviolet-Evoked Prostaglandin Formation Protect Skin From Actinic Cancer?** (Eng)



aves, M. W. (Inst. Dermatology, St. John's Hospital, London E9 6BX, England). *Lancet* 1(8057): 189-189; 1978.

ole for prostaglandin formation in protecting individuals against skin cancer is proposed. A fall in cellular cyclic AMP (cAMP) and a rise in cyclic guanosine monophosphate has been reported in cell culture systems with active proliferation; cellular transformation has also been associated with lower cellular concentrations of cAMP. Prostaglandins increase dermal cAMP levels in normal skin in vitro and, to a much lesser extent, in psoriatic skin, in which cAMP is usually reduced. Prostaglandin E has been shown to reduce the growth rate of HeLa cells and B-16 mouse melanoma cells in vitro. It is thus suggested that raised levels of prostaglandin in UV-irradiated human skin could protect epidermal cells against the mutagenic effects of UV by increasing cAMP formation, thus reducing the vulnerable pool of actively dividing cells. (18 refs)

1244 **A Review of the Studies on the Genetic Effects of the Atomic Bombs in Japan (Meeting Abstract).** (Eng) Neel, J. V. (Dept. Human Genetics, Univ. Michigan Medical Sch., Ann Arbor, MI). *Clin Genet* 13(1): 130; 1978. (no refs)

1245 **Repair Deficient Human Disorders and Cancer.** (Eng) Setlow, R. B. (Biology Dept., Brookhaven National Lab., Upton, NY, 11973). *Nature* 271(5647): 713-717; 1978.

Studies of DNA repair defects in patients suffering from xeroderma pigmentosum (XP), ataxia telangiectasia (AT), and Fanconi's anemia (FA), all of whom are cancer prone, are reviewed. All XP cell lines are defective in one or more repair pathways for UV damage to DNA, suggesting that UV-induced skin carcinogenesis in normal persons has a low probability because most of the lesions are removed, and DNA synthesis beyond any that remain is relatively error free. In excision-defective XP cells, many pyrimidine dimers remain, and replication beyond them makes an appreciable number of mistakes, giving a high possibility for neoplastic transformation. All AT cell lines investigated were proficient in the repair of single- and double-strand breaks, but half of them were defective in repair replication following anoxic irradiation. Repair defects in AT also include chemical damage in addition to x-ray damage. FA cells appear to be defective in the repair of cross-links, and they may also be slightly defective in the repair of  $\gamma$ -ray and UV damage. The molecular nature of the defects in DNA repair seen in these syndromes suggests that unrepaired damage to DNA has a high carcinogenic potential. Even in normal individuals, the rate of DNA repair compared with other cellular processes should be an important parameter in the initial steps in carcinogenesis. (100 refs)

78-1246 **DNA Repair and Human Disease. The Case of Xeroderma Pigmentosum.** (Eng) Kacinski, B. M. (Training Program, Yale Univ. Sch. Medicine, New Haven, CT). *Conn Med* 42(2): 99-104; 1978.

The basic biochemistry of DNA repair in xeroderma pigmentosum (XP) is presented, and theories attempting to correlate the molecular pathology of XP with its clinical symptoms are reviewed. Special attention is focused on DNA repair in XP and in its more severe form, the DeSanctis-Cacchione syndrome. (12 refs)

78-1247 **Xeroderma Pigmentosum: Recent Studies on the DNA Repair Defects.** (Eng) Friedberg, E. C. (Dept. Pathology, Stanford Univ., Stanford, CA 94305). *Arch Pathol Lab Med* 102(1): 3-7; 1977.

Studies demonstrating the complexity of the DNA repair defect in xeroderma pigmentosum (XP) cells are reviewed. In addition to their inability to carry out repair synthesis after exposure to UV light, XP cells are also defective in the repair of DNA damage caused by 4-nitroquinoline 1-oxide, bromobenz(a)anthracene, and acetylaminofluorine. Not all results are consistent with the nucleotide excision-repair mode, which suggests that the XP defect may also involve a base excision-repair mode, in which damaged bases are removed by the action of glycosidase followed by endonucleolytic attack at the sites of base loss. (47 refs.)

78-1248 **Mutagenicity Detection with Human Cells.** (Eng) DeMars, R. (Lab. Genetics, Univ. Wisconsin, Madison, WI, 53706); Jackson, J. L. *J Environ Pathol Toxicol* 1(2): 55-77; 1977.

Mutagenesis detection methods for five loci can be used with cultured human cells. Selections with  $\alpha$ -amanitin and ouabain specifically detect missense mutations. Azaguanine selection detects any mutation that reduces hypoxanthine-guanine phosphoribosyltransferase activity, but it does not detect mitotic recombination and karyotype changes. Mutations affecting two autosomal loci are detectable by selection with diaminopurine and with antibodies against the histocompatibility SD antigens. These mutation detection systems respond to chemical mutagens and/or radiation. Calibrations of single-locus mutation rates with general indicators of genetic damage, such as DNA repair, can be performed with human cells, and then may make it possible to evaluate the mutagenicity of substances as induced DNA repair. Histochemical techniques could also be used to improve mutation studies: missense mutations affecting glucose-6-phosphate dehydrogenase can be quantified by counting cells that reduce tetrazolium with a substrate analog, 2-deoxyglucose-6-phosphate. Mutations affecting the autosomal 'I' locus, which cause multiple deficiencies of lysosomal



enzymes, can be quantified as cells that stain intensely for acid phosphatase. Thioguanine-resistant lymphocytes can be quantified directly upon their removal from the body after mutagenic insults. These methods should make it possible to evaluate genetic damage to body cells under the conditions in which they encounter mutagens in vivo. (41 refs)

- 78-1249 Defective and Nondefective Ad2-SV40 Hybrids.** (Eng) Lewis, A. M. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014). *Prog Med Virol* 23: 96-139; 1977.

Defective and nondefective Ad2-SV40 hybrids have been selected from a strain of human adenovirus 2 (Ad2) adapted to grow in rhesus monkey cells containing simian virus 40 (SV40). These recombinants contain from 7% to 239% of the SV40 genome inserted in three different locations in the Ad2 genome, and they are accompanied by Ad2 DNA deletions varying between 4.5% and 40%. Studies of the defective Ad2-SV40 hybrids have defined the extent of the interactions between the genomes of these unrelated viruses in dually infected cells and suggested a mechanism by which integrated viral genomes may be excised. Studies of nondefective Ad2-SV40 hybrids have associated specific regions of the SV40 genome with the induction of early SV40 antigens, polypeptides, and biological functions, including the induction of malignant disease in hamsters. Studies of tumor induction in hamsters by UV-inactivated hybrids imply that the entire early region of the SV40 genome must be present and functioning before SV40 carcinogenesis is conveyed to the recombinant genome. Such an interpretation would confirm other results, which indicate that the entire A-gene region in SV40 temperature-sensitive mutants must function to induce and maintain the phenotype of the SV40-transformed cell. (105 refs)

- 78-1250 Evolutionary Variants of Simian Virus 40.** (Eng) Brockman, W. W. (Dept. Microbiology, Univ. Michigan Medical Sch., Ann Arbor, MI, 48109). *Prog Med Virol* 23: 69-95; 1977.

Simian virus 40 (SV40) is reviewed based on information accumulated from progeny virus that evolve when SV40 is serially passaged at a high multiplicity of infection in permissive cells. A key event in the transformation of nonpermissive cells is the incorporation of SV40 DNA into the host cell DNA. However, a cell that is already transformed can also incorporate more SV40 DNA. Integration of SV40 DNA into the host genome is not always site specific. Special attention is focused on the physical genome map, viral genetics, the cloning of evolutionary variants of SV40, the characterization of complementing and substituted variants, initiation and termination of DNA replication in evolutionary variants, processes underlying the evolution of SV40 variants, and biological activities of complementing variants. (70 refs)

- 78-1251 RNA Tumor Viruses: Getting a Handle on Transformation.** (Eng) Marx, J. L. (No affiliation given). *Science* 199(4325): 161-164; 1978.

A review of some of the experimental work on C-type RNA tumor viruses is presented. The avian sarcoma virus (Rous sarcoma virus) contains a gene (*src*) that codes for a protein product that must be formed for transformation to occur. However, the function of the *src* gene and its products may not be limited to transformed cells: cells from all vertebrate species examined in one laboratory have one or a few DNA sequences related to the *src* gene. Thus the *src* gene might perform some essential function in normal cells, such as regulation of cell division. The sarcoma virus could thus have originated by incorporation of the *src* gene into a precursor virus. Other studies have shown that about 15% of the RNA of the sarcoma virus derived from Kirsten leukemia virus and leukemia virus RNA and the remainder consists of endogenous C-type viral sequences originating in the rat. Transformation could thus result from recombination of an ecotropic virus and a xenotropic virus or a recombination involving envelope genes. Mink cell focus-inducing viruses are an example of the former, and they may cause leukemia in AK mice. (no refs)

- 78-1252 Oncornaviruses Type D and Their Possible Role in Neoplastic Processes.** (Eng) Yershov, F. (D. I. Ivanovsky Inst. Virology, Moscow, USSR); Zhdanov, V. M. *Prog Med Virol* 23: 140-157; 1977.

Current knowledge on human tissue D-type oncornaviruses (HTOD) is reviewed. Homology experiments indicate that HTOD is an exogenous oncornavirus for humans. The virus is similar to another D-type oncornavirus isolated from simian tissues, but the two are not quite identical in their biological characteristics. The RNA and DNA from HTOD react with the DNA and RNA from virus-producing cultures and from hormone-associated (mammary and ovarian) cancers in humans. In 50% of these human cancers, a simultaneous detection test was positive. In one of these cases, RNA from the milk of a mammary cancer patient was homologous to DNA from HTOD; a simultaneous detection test was also positive. When the tumor was removed, sequences homologous to HTOD DNA were found in the tumor DNA, and the simultaneous detection test was positive. Particles resembling HTOD have been found in the milk of mammary cancer patients and healthy women from cancer families. Other topics discussed include the molecular biology of the virus, and the cellular and viral aspects of their potential role in neoplastic transformation. (81 refs)

- 78-1253 Viruses and Cancer.** (Eng) Winters, W. D. (Dept. Microbiology, Univ. Texas Health Science Center, San Antonio, TX). *Am J Nurs* 78(2): 249-251; 1978.



The potential role of viruses in human cancers is surveyed. Although there is no evidence for a causal association, tumor-associated antigens have been detected in some human tumors. There is also evidence that viruses may react with other agents, such as chemicals, to trigger neoplastic change. (27 refs)

**78-1254 Hypotheses on Viral Carcinogenesis.** (Ita) Sforza, M. (Istituto di Clinica Chirurgica e Terapia Chirurgica, Università di Modena, Modena, Italy); Perelli Ercolini, M.; D'Alessandro, G. *Arch Sci Med (Torino)* 134(4): 399-401; 1977.

Various causes of neoplasia are discussed with particular reference to viruses. It is felt that neoplasia arises from a variety of etiologies, mostly of an irritative nature, coupled with a single, final pathogenetic stage involving chromosome changes that do not result in cell death. (2 refs)

**78-1255 Is the Polio Virus Responsible for Late Central Nervous System Tumors?** (Eng) Ohry, A. (Neurological Rehabilitation Dept., Chaim Sheba Medical Center, Tel-Hashomer, Israel); Brooks, M. E.; Rozin, R. *Med Hypotheses* 4(1): 44-49; 1978.

A hypothesis relating poliomyelitis viruses and late-developing neoplasia in the CNS has been developed as a result of some clinical observations and a literature survey. Two female patients with spinal cord tumors (neurogenic sarcoma and meningioma) developing 30 yr after childhood poliomyelitis were seen in the same year, and this started the search for an etiological relationship. There is evidence of polio virus causing destruction of nerve cells, an immune reaction, and late motor neuron disease. If a slow viral infection, such as the polio virus, is the etiological agent in neurogenic tumors, the problem must be attacked epidemiologically, because electron microscopic, histologic, serologic, or immunologic techniques may fail to identify the agent. The white population has a high incidence of poliomyelitis, CNS tumors, and multiple sclerosis; the next question is whether there is a relationship among these diseases. (49 refs)

**78-1256 Viral Etiology of Cancer and Leukemia: A Look into the Past, Present, and Future--G. H. A. Clowes Memorial Lecture.** (Eng) Gross, L. (Cancer Res. Unit, Veterans Admin. Hosp., Bronx, NY 10468). *Cancer Res* 38(3): 485-493; 1978.

Studies of the experimental transmission of oncogenic viruses are reviewed. These viruses are common in many animal species, presumably including man, and they have probably been transmitted as a latent infection from generation to genera-

tion for millions of years. If activated by metabolic, hormonal, or chemical factors or by ionizing radiation, the latent viruses acquire pathogenic potential and cause the development of tumors or leukemia. The viruses are probably incorporated in the genetic cell material of their hosts, although they could be carried in a submerged form that is undetectable by current laboratory techniques. Essentially, however, the viruses are similar to other infectious agents characterized by host-to-host transmission. Thus, the law of obligate communicability would apply not only to communicable diseases but to tumors, leukemias, and slow virus diseases (eg, scrapie in sheep and kuru or Creutzfeldt-Jakob disease in humans). The epidemiologic and immunologic aspects of oncogenic viruses and slow virus diseases are among the most challenging problems in experimental medicine. (87 refs.)

**78-1257 Viruses Associated with Renal Disease of Man and Animals.** (Eng) Morrison, W. I. (International Lab. Res. on Animal Diseases, P.O. Box 30709, Nairobi, Kenya); Wright, N. G. *Prog Med Virol* 23: 22-50; 1977.

The role of viruses in renal disease of man and animals is reviewed with particular reference to the pathogenetic mechanisms. Although few viruses have been implicated in clinical renal disease, lymphocytic choriomeningitis virus, lactic dehydrogenase virus, murine leukemia viruses, Aleutian disease virus, equine infectious anemia virus, and hepatitis B virus have been associated with immune complex glomerulonephritis. (145 refs)

**78-1258 Limited Immunodeficiency.** (Eng) Anonymous (No affiliation given). *Lancet* 1(8056): 132-133; 1978.

The proliferation of T cells in patients with Duncan's disease associated with Epstein-Barr virus (EBV), which can terminate in fatal infectious mononucleosis, is contrasted with the proliferation of B cells in Duncan's disease patients with Burkitt's lymphoma or plasmacytoma. The stimulation of T cells by EBV antigens is usually followed by lifelong immunity and positive cell-mediated responses to EBV. The behavior of the B cells is similar to that of EBV-infected cell lines and, after several years, the cells become malignant. (20 refs.)

**78-1259 The HLA System and Immunological Defence Against Cancer: A Review.** (Eng) Oliver, R. T. (Imperial Cancer Res. Fund, Dept. Medical Oncology, St. Bartholomew's Hosp., London EC1, England). *J R Soc Med* 71(1): 50-54; 1978.

The long evolutionary history of the major histocompatibility system and the occurrence of human lymphocyte antigen



(HLA) and disease associations make it likely that the real biological importance of the HLA system is in determining resistance/susceptibility to infectious and malignant disease. In nonmalignant disease, two mechanisms have been implicated in the association of HLA antigens with disease. In ankylosing spondylitis, evidence is accumulating for cross tolerance between a bacterial antigen and the HLA-B27 antigen, but in the autoimmune diseases, the involvement of an abnormal immune response (Ir) gene, associated with the A1/B8 haplotype, is strongly suspected. The same haplotype has also been associated with recovery from hepatitis B infection and survival of patients with Hodgkin's disease and acute myeloid leukemia. Weak associations have been reported of HLA-A2 with acute lymphoblastic leukemia and A10 with breast carcinoma. The A1/B8 haplotype has been associated with enhanced immunoresponsiveness in the studies of HLA antigens in nonmalignant disease; it is possible that the same mechanism is responsible for its influence on survival in Hodgkin's disease and acute myeloid leukemia. (20 refs)

- 78-1260 **Immunological Aspects of Aging.** (Dut) Hijmans, W. (Instituut voor Experimentele Gerontologie, Gezondheidsorganisatie TNO, Lange Kleiweg 151, Rijswijk, Netherlands). *Ned Tijdschr Geneesk* 121(42): 1650-1652; 1977.

Aging is accompanied by an impairment of cellular and humoral immunity. Immunological reactions appear to play a role in the defense against malignant tumors, which would explain the increase in cancer incidence with aging. (4 refs.)

- 78-1261 **Is There an Immunological Explanation for the Increased Cancer Incidence in Old Age?** (Dut) Rumke, P. (Sectie Immunologie, Antoni van Leeuwenhoekhuis, Het Nederlands Kanker Instituut, Sarphatistrasse 108, Amsterdam, Netherlands). *Ned Tijdschr Geneesk* 121(42): 1654-1656; 1977.

General relationships among cellular immunity, aging, and cancer are reviewed. Nude mice without T-cell-mediated immunity are not predisposed to spontaneous or chemically induced tumors; they are only susceptible to virus-induced tumors. The findings were similar for animals that received immunosuppressive treatment. Kidney transplant patients on long-term immunosuppressive therapy are susceptible to certain types of tumors, mainly of the immune system, that may be of viral etiology. The development of these tumors may be due to less efficient virus elimination. There are no significant immunological differences between in vitro and in vivo spontaneous tumors. The failure of immunological tumor surveillance may be a result of serum factors blocking the cellular immune response. The reduced efficiency of virus elimination because of impaired T-cell function in senescence can be considered a possible cause of increased tumor inci-

dence in old age, but the age-dependent accumulation of carcinogens in the body also plays an important role. Nonimmunological factors may be more important than immunological ones in the increased incidence of malignant tumors in senescence. (6 refs.)

- 78-1262 **A Mechanism of Tumorigenesis. Retrodifferentiation and Reontogeny in Cancer and Its Clinical Significance.** (Eng) Longenecker, J. P. (Dept. Biochemistry, Sch. General Studies, Australian Natl. Univ., P.O. Box 1, Canberra City, ACT 2600, Australia); Williams, J. F. *Med J Aust* 2(8): 237-239; 1977.

Data on gene expression in malignant growth that are supportive of a retrodifferentiation theory of tumorigenesis are reviewed. The gene products discussed fall into three categories: antigens and related immunology, ectopic hormones and ectopic isoenzymes. Most if not all neoplasms, regardless of their adult tissue of origin, apparently reexpress genes associated with embryonic developmental structures appearing as early as the trophoblast. It is suggested that permanent reexpression of the early developmental genes may be necessary to maintain malignancy. The similarities at the molecular level among neoplastic, embryonic, and regenerating tissue are discussed. Further identification of the proteins associated with early developmental genes may lead to improved clinical management of the cancer patient. (39 refs)

- 78-1263 **Pathogenesis of Cancer.** (Spa) Valladares, Y. (Departamento de Biología y Bioquímica de Cáncer, Instituto Nacional de Oncología, Ciudad & Universitaria, Madrid-3, Spain). *Rev Esp Oncol* 24(1): 223-264; 1977.

Studies of physical, chemical, and biological carcinogenic factors, their mechanisms of action, and the biological aspects of malignant transformation at the molecular level are reviewed. (no refs.)

- 78-1264 **The Role of the Microcirculatory System in Metastasis.** (Rus) Chernukh, A. M. (Inst. General Pathology and Pathophysiology, Moscow, USSR); Shilov, V. S. *Vestn Akad Med Nauk SSSR* (10): 29-33; 1977.

Current data on the role of the microcirculatory system in the metastatic spread of tumor cells are reviewed. Simulation of microcapillary damage with UV laser radiation in rats inoculated with ascites Zajdela hepatoma cells resulted in a 70% increase of tumor cell sedimentation in these vessels. (3 refs)

- 78-1265 **Teratocarcinoma Cells and Normal Mouse Embryogenesis.** (Eng) Graham, C. F. (Dept. Zool



Univ. Oxford, Oxford, England). In: *Concepts in Mammalian Embryogenesis*. Sherman, M. I., ed. (Cambridge, MA: MIT Press): Cell Monograph Series No. 1, 404 pp.; 315-394; 1977.

appearance of teratocarcinomas during normal mouse embryogenesis is reviewed. The embryo forms teratocarcinomas more frequently as it develops, up to the late egg-lar stage on day 8 of pregnancy. This increasing frequency up to day 8 is probably due to an increase in the ability of pluripotential cells in the embryo to survive and form embryonic ectoderm in extrauterine sites as they grow larger. Specific attention is focused on spontaneous teratocarcinomas, chromosomal abnormalities and their effects on development, a comparison of the differentiation of embryonic carcinoma cells and embryos, stem cell development, a comparison of embryonic carcinoma cells and other tumor cells, induction of teratocarcinomas, and cessation of embryonic carcinoma cell proliferation by differentiation. (304 refs)

1266 **Prolactin and Breast Cancer.** (Eng) Schyve, P. M. (Illinois State Psychiatric Inst., Chicago, IL); Rothline, F.; Meltzer, H. Y. *Psycho Pharmacol Bull* 14(1): 19; 1978.

A possible association of prolactin with human mammary cancer is reviewed. In rodents, elevated plasma prolactin levels are associated with a high incidence of 7,12-dimethylbenz(a)anthracene-induced tumors, and in one strain of mice, elevated plasma prolactin levels increase the incidence of spontaneously developing adenocarcinomas. However, prolactin is leutotropic in rats, but not in humans; in rats, the tumors are adenocarcinomas and they rarely metastasize, but in humans, they are scirrhous and they will metastasize. Studies with humans have failed to establish an association between increased plasma prolactin levels and breast cancer. However, up to 30% of human breast tumors may be prolactin dependent. The use of prolactin-stimulating antipsychotics may be contraindicated in these patients. (32 refs)

1267 **Breast Cancer: Potentially Predisposing and Protecting Factors. Role of Pregnancy, Lactation, and Endocrine Status.** (Eng) Vorherr, H. (Dept. Obstetrics-Gynecology and Pharmacology, 915 Stanford Drive E., Univ. New Mexico, Sch. Medicine, Albuquerque, New Mexico, 87131); Messer, R. H. *Am J Obstet Gynecol* 130(3): 535-538; 1978.

Genetic and nonfamilial factors that predispose to breast cancer and factors that protect against the disease are discussed in detail. The risk of breast cancer has been correlated with the availability of estradiol and estrone. In the presence

of sufficient estradiol, estrone cannot reach the nucleus of estrogen target tissues for the stimulation of cell proliferation. In postmenopausal women, the lack of estrone-opposing estradiol and progesterone may result in estrone-induced hyperstimulation and neoplastic change. Other mechanisms protecting against breast cancer are thought to be due to the mitotic rest of the mammary epithelium (low DNA synthesis), as encountered during pregnancy and lactation. (212 refs)

78-1268 **Hereditary Adenocarcinomatosis over Four Generations in a Family from Valais, Switzerland.** (Fre) Dubosson, J. D. (Institut de Genetique medicale, 8, chemin Thury, 1206 Geneva, Switzerland). *J Genet Hum* 25(4): 233-278.

Four generations of a family from the canton of Valais, Switzerland, have been afflicted with hereditary adenocarcinomatosis, and the case reports of the 22 affected members are given. Twenty-one of the patients were from the first three generations (47 members), and they had a total of 26 tumors. These included adenocarcinomas of the colon (16), stomach (2), rectum (1), and duodenum (1); 1 papillary carcinoma of the ovary, 1 osteosarcoma, 1 cutaneous fibrosarcoma, 1 glioblastoma multiforme, 1 basal cell carcinoma, a cerebral metastasis of unknown primary origin, and 1 tumor of the biliary tract. The 22nd patient, a girl aged 21, was from the fourth generation (32 members), and she had an adenocarcinoma of the colon with multiple polyps. At age at tumor appearance was 45 yr. Hereditary transmission was autosomal dominant, with a predilection for the male sex: 57.1% of the men and 26.3% of the women were affected. The different familial forms of cancer, including their precancerous conditions, are reviewed. (59 refs)

78-1269 **The Epidemiology of Thyroid Cancer.** (Eng) Williams, E. D. (Dept. Pathology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales). *Ann Radiol (Paris)* 20(8): 722-724; 1977.

A review of the epidemiology of the different types of thyroid cancer is presented. Follicular carcinoma is more common in areas with endemic goiter (iodide deficiency) than in those where goiter is not as common. Papillary carcinoma, the most common of the thyroid cancers, is most common in areas with excess iodide intake. It is suggested that part of the increasing frequency of papillary carcinoma may be related to increasing dietary intake of iodide. Radiation is also a significant factor in the etiology of papillary carcinoma, especially in children. Anaplastic carcinoma is primarily a disease of the elderly. Histologic studies have indicated that these tumors regularly show evidence of preexisting differentiated



thyroid carcinoma. Therefore, the incidence of anaplastic carcinoma may be related to the incidence of differentiated tumors and to the occurrence of factors that lead to a change in the malignancy and differentiation of these tumors. As many as 20% of all medullary carcinomas of the thyroid may have a genetic basis. Furthermore, the epidemiology may be related to calcium rather than iodide metabolism. Malignant lymphoma of the thyroid occurs most frequently in association with severe thyroiditis, and it is more common in areas where thyroiditis is more common. (29 refs)

**78-1270 Epidemiology of Thyroid Cancer.** (Eng) Sancho-Garnier, H. (Service de Statistique, Institut Gustave-Roussy, 16 av. Paul-Vaillant-Couturier, F 94800 Villejuif, France). *Ann Radiol (Paris)* 20(8): 715-721; 1977.

The frequency and distribution of thyroid carcinomas are reviewed and etiological hypotheses discussed. Data from a large number of cancer registries indicate that thyroid carcinoma is a rare tumor, with an annual incidence of 0.3-15/100,000, and that women are much more susceptible than men. There is an increasing incidence with advancing age that is particularly striking in men. Epidemiological studies, as well as animal experiments, have confirmed that ionizing radiation can produce thyroid tumors, both benign and malignant, that the risk is dose-dependent, and that the risk is inversely proportional to age at radiation exposure. There is also a significant relationship between alcohol consumption and thyroid cancer for both sexes and age group, regardless of tobacco habits. The female predominance that is seen in all geographical locations suggests that some hormonal factor has an etiological role in these cancers. (16 refs)

**78-1271 Regulation of Differentiation in Normal and Transformed Erythroid Cells.** (Eng) Rifkind, R. A. (West 168 St., Columbia Presbyterian Medical Center, New York, NY, 10032); Marks, P. A.; Bank, A.; Terada, M.; Reuben, R. C.; Maniatis, G. M.; Fibach, E.; Nudel, U.; Salmon, J. E.; Gazitt, Y. *In Vitro* 14(1): 155-161; 1978.

Data on murine erythroleukemia cell (MELC) differentiation are reviewed with respect to the nature of chemical inducing agents, early metabolic events related to differentiation, requirements for stable commitment to differentiation, and the accumulation of globin messenger RNA (mRNA), globin synthesis, and other factors involved in globin gene expression during differentiation. In addition to dimethyl sulfoxide, planar-polar compounds such as N-methylacetamide and the polymethylene bisacetamides also induce differentiation. There is evidence that the plasma membrane and membrane-associated functions play an important role in the induction

of MELC differentiation, but this role is not definite. The proportion of cells in culture committed to differentiation depends on both the concentration and duration of exposure to the inducing agent. Furthermore, DNA synthesis is necessary but not sufficient factor for the induction of differentiation. It is suggested that the observed differences in the ratio of B-major and B-minor globins are not due to changing rates of globin synthesis at different stages of differentiation. The inducers appear to control these rates, affecting the transcription or processing of mRNA for the proteins. It thus appears that differentiation involves an early change in the cell membrane, a prolongation of G<sub>1</sub>, with chromatin and DNA alterations, a programming of chromatin for transcription of erythroid cell-specific gene products, and stabilizing events that render the differentiation irreversible. (54 refs)

**78-1272 Replication Origins.** (Eng) Sherratt, D. (School of Biological Sciences, Univ. Sussex, Sussex, England). *Nature* 271(5644): 404-405; 1978.

Current data on the replication origins of DNA polymerases which are unable to initiate polynucleotide chains de novo are reviewed. Initiation of replication appears to be controlled by replicon-specific signals that allow or prevent replication. These signals (proteins) appear to be enzymes that nick DNA but conserve the phosphodiester bond energy by becoming covalently bound to the 5' end of the nicked strand; they are subsequently able to religate the 5' end to the original or new 3'OH with little or no further energy input. DNA nicking-closing enzymes are similar to these enzymes. One of the nicking-closing enzymes is *Escherichia coli* DNA gyrase which induces negative superhelical turns in vivo into covalently closed DNA. In vitro, it can introduce negative superhelicity, remove superhelical turns, and cleave specific phosphodiester bonds. These properties make it and similar rejoining enzymes candidates for involvement in recombination and transposition. (9 refs)

**78-1273 Cancer: Clues in the Mind.** (Eng) McQuerry, G. (Univ. Missouri at Columbia, Columbia, MO). *Sci News* 113(3): 44-45; 1978.

Studies that suggest a psychosomatic basis for cancer and correlation between depression and reduced immune competence are reviewed. The data indicate that cancer tends to occur more frequently in persons who are unable to express anger or resentment or who are subjected to chronic emotional stress, psychic trauma, or a sense of personal failure. (refs.)



## CHEMICAL CARCINOGENESIS

274 **Mutagenicity of Carcinogenic Mycotoxins in *Salmonella typhimurium*.** (Eng) Ueno, Y. (Lab. Microbial Chemistry and Toxicology, Faculty Pharmaceutical Sciences, Tokyo Univ. Science, Ichigaya, Shinjuku-ku, Tokyo 162, Japan); Kubota, K.; Tashiro, F.; Ito, T.; Yamura, Y. *Cancer Res* 38(3): 52-58; 1978.

Mycotoxins and chemically modified toxins were tested for mutagenic activity in the His- revertant assay using *Salmonella typhimurium* TA98 and TA100. Bisfuranoid mycotoxins such as aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), aflatoxin G<sub>1</sub>, sterigmatocystin, and O-acetylsterigmatocystin were positive in the Ames test method. Epoxide mycotoxins such as PR-toxin and crotoxin were positive only when the test strains were incubated with the mycotoxins in the presence of the fortis-S-9 fraction (supernatant fraction, 9,000 x g for 20 min). Anthraquinoid hepatocarcinogens such as (-)-luteoskyrin and emarginin; lactones such as citrinin, penicillic acid, and aflatoxin; and chlorinated carcinogens such as chloroacetate, aflatoxin, and aflatoxin were negative in both the routine and preincubation assay methods. *Fusarium* mycotoxins such as the trichothecenes and zearalenone also failed to demonstrate mutagenicity. However, crotoxin, a bis-epoxide trichothecene, enhanced the mutagenicity of AFB<sub>1</sub>. In vitro addition of glutathione (GSH) to the S-9 mixture also enhanced the mutagenicity of AFB<sub>1</sub>, but prior administration of various hepatotoxic agents (chloroacetate, methylmercury chloride, carbon tetrachloride) to rats reduced the S-9-dependent mutagenicity of AFB<sub>1</sub>. Organ and species variations of AFB<sub>1</sub> mutagenicity were examined in normal rats, guinea pigs, mice, and mice. The results indicated that factors such as epoxide hydrolase, GSH-epoxide transferase, free GSH, and protein may control the exact nature of AFB<sub>1</sub> mutagenicity. (17 refs)

1275 **Complement Activity, Serum Protein, and Hepatic Changes in Guinea Pigs Given Sterigmatocystin or Aflatoxin, Alone or in Combination.** (Eng) Schard, J. L. (Natl. Animal Disease Center, North Central Region, Agricultural Res. Service, Ames, IA, 50010); Thurman, J. R.; Lillehoj, E. B.; Cysewski, S. J.; Booth, G. D. *Am J Vet Res* 39(1): 163-166; 1978.

The effects of sterigmatocystin (SCM: 4.2 mg/day) and aflatoxin B<sub>1</sub> (AFB<sub>1</sub>: 0.01 mg/day), either alone or in combination, on the complement activity and serum proteins of male guinea pigs were determined. Although changes in total serum protein were not marked in any animals, SMC and AFB<sub>1</sub> alone significantly decreased  $\alpha_2$ -globulin. The combination of toxins significantly increased serum albumin and significantly decreased both  $\alpha_1$ - and  $\beta$ -serum globulins. SCM depressed complement activity, but not significantly.

However, SCM + AFB<sub>1</sub> significantly reduced complement activity. Pigs given SCM had a diffuse fatty degeneration of the hepatocytes and focal necrosis without any particular lobular distribution. Changes in pigs given both toxins varied from diffuse fatty change with mild ductal hyperplasia to mild bile duct hyperplasia only. Liver sections from pigs given AFB<sub>1</sub> alone were unaltered. No kidney changes were noted in any of the treated animals. (17 refs)

78-1276 **Interaction of Aflatoxin B<sub>1</sub> with Transfer Ribonucleic Acids.** (Eng) Aboobaker, V. S. (Biochemistry and Food Technology Div., Bhabha Atomic Res. Centre, Bombay 400 085, India); Bhattacharya, R. K. *Indian J Biochem Biophys* 14(3): 296-298; 1977.

The physical binding of aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) to transfer RNA (tRNA) from rat liver and *Escherichia coli* K12 was investigated. tRNA from both sources brought about a perturbation in the absorption of AFB<sub>1</sub> in a manner similar to that of DNA. However, polyribosomal guanine (poly rG) was more reactive than DNA or either of the tRNA's; ie, it showed max binding. A Scatchard plot of the binding of AFB<sub>1</sub> to both tRNA's, DNA, and poly rG was linear, indicating the involvement of one binding process in the formation of the AFB<sub>1</sub> complex. Extrapolation of these findings indicated that the number of binding sites per 100 nucleotides was 0.65 for rat liver tRNA, 0.60 for *E. coli* tRNA, 1.10 for calf thymus DNA, and 1.20 for poly rG. The respective association constants for the binding of the nucleic acids was 1.54, 1.33, 0.94, and  $2.50 \times 10^4/M$ , respectively.  $Mg^{+2}$  concentrations of 2 mM and  $Na^{+}$  concentrations  $\geq 50$  mM reversed AFB<sub>1</sub> binding; the magnitude of these effects was stronger for DNA than for tRNA. It is suggested that guanine is mainly responsible for the binding of AFB<sub>1</sub>, since only poly rG showed max binding. (15 refs)

78-1277 **In Vitro Metabolism of Aflatoxin B<sub>2</sub> by Animal and Human Liver.** (Eng) Roebuck, B. D. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH, 03755); Siegel, W. G.; Wogan, G. N. *Cancer Res* 38(4): 999-1002; 1978.

The pathways by which aflatoxin B<sub>2</sub> (AFB<sub>2</sub>) is metabolized by male Peking duck, male Fischer CDF rat, male White Swiss CFW mouse, and human liver were studied in vitro. Duck liver had a much higher level of activity than tissues from other species. Postmitochondrial supernatant equivalent to 0.2 g whole liver metabolized 40%-80% of the initial substrate in 30 min, compared with <6% for the other spe-



cies. Among the metabolites formed by duck liver, AFB<sub>1</sub> was produced in amounts equivalent to 2%-8% of the initial substrate, and metabolites having chromatographic properties postulated for aflatoxins 1 and 2 and AFM<sub>1</sub> and AFM<sub>2</sub> were also formed in small amounts. In contrast, rat, mouse, and human liver preparations produced no detectable AFB<sub>1</sub> and only small amounts of compounds thought to be AFQ<sub>1</sub> and AFP<sub>2</sub>. The greater susceptibility of duck liver to the toxicity of AFB<sub>1</sub> may be due to its ability to form AFB<sub>1</sub>, which could then be activated through further metabolism. (16 refs)

- 78-1278 **Aflatoxin Metabolism and Absence of Cytochrome P-450 in Rat Colon Tissue During Vitamin A Malnutrition.** (Eng) Adekunle, A. A. (Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria); Campbell, T. C.; Campbell, S. C. *Experientia* 34(2): 230-232; 1978.

Metabolic studies of aflatoxin B<sub>1</sub> (AFB) were performed using homogenized colon mucosal linings from vitamin A-adequate and -deficient male Sprague-Dawley rats. The homogenates from both rat groups did not contain any cytochrome P-450, but a pigment with a CO-difference-spectrum absorption max at 420 nanometers was identified. This pigment was tentatively identified as P-420, and it was significantly higher in the colon mucosa of vitamin A-deficient animals than in vitamin A-adequate animals. There was no significant difference in the residual AFB in both groups. The mucosal epithelium of all colons, despite their lack of cytochrome P-450, were capable of metabolizing AFB to AFR<sub>0</sub>, AFQ<sub>1</sub>, and AFM<sub>1</sub>. The deficient animals metabolized more AFB to the component products, although the difference was not significant. There were, however, significant differences in the amount of AFR<sub>0</sub>. It is probable that the colon epithelium contains a pigment (other than cytochrome P-450) that has a higher activity in vitamin-deficient animals. (14 refs)

- 78-1279 **Methylxanthine Inhibition of Aflatoxin Production.** (Eng) Buchanan, R. L. (Dept. Nutrition and Foods, Drexel Univ., Philadelphia, PA, 19104); Fletcher, A. M. *J Food Sci* 43(2): 654-655; 1978.

The effects of caffeine and theophylline on growth and aflatoxin B<sub>1</sub> production by *Aspergillus parasiticus* NRRL 2999 were studied in AMY medium (glucose + mineral salts + yeast extract) at pH 4.5. Caffeine levels of 0.5, 1.0, and 2.0 mg/ml decreased aflatoxin production by 86%, 96%, and 100%, respectively. Theophylline levels of 2.0, 4.0, and 8.0 mg/ml were tested, but only the highest concentration was inhibitory, decreasing aflatoxin production by 54%. Inhibition of growth was observed, but it did not completely account for the reduction in aflatoxin production. These findings may explain why aflatoxins are not usually isolated from caffeine-containing commodities, and they suggest that extra

precautions should be taken to insure that decaffeinated coffee products are stored under conditions that will prevent the growth of aflatoxigenic molds. The preferential inhibition of aflatoxin production by caffeine suggests that aflatoxin biosynthesis is influenced by the cyclic AMP concentration within the cell. The differential response between caffeine and theophylline may be due to theophylline being less effective as a phosphodiesterase inhibitor or affecting the enzyme via a different mechanism. (19 refs)

- 78-1280 **7,8-Benzoflavone (BF) Stimulates the Metabolic Activation of Aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) to Mutagens by Human Liver (Meeting Abstract).** (Eng) Buening, M. K. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ, 07110); Fortner, J. G.; Conney, A. H. *Fed Proc* 37(3): 749; 1978. (no refs)

- 78-1281 **Effect of Cyclopropene Fatty Acids on Aflatoxin in Metabolism in Rainbow Trout (Meeting Abstract).** (Eng) Loveland, P. M. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR, 97331); Nixon, J. E.; Eisele, T. A.; Pawlowski, N. E.; Sinnhuber, R. *Fed Proc* 37(3): 506; 1978. (no refs)

- 78-1282 **Carcinogenicity of Aflatoxin Q<sub>1</sub> to Rainbow Trout and its Potentiation by Cyclopropene Fatty Acids (Meeting Abstract).** (Eng) Hendricks, J. D. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR, 97331); Sinnhuber, R. O.; Nixon, J. E.; Wales, J. H.; Putnam, G. B.; Loveland, P. M.; Masri, M. S.; Hsieh, D. *Fed Proc* 37(3): 451; 1978. (no refs)

- 78-1283 **Effects of Aflatoxins on ATPase Activities in Rat and Mouse Tissues (Meeting Abstract).** (Eng) Desai, D. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS, 39216); Phillips, T. D.; Hayes, A. W.; Ho, I. K. *Fed Proc* 37(3): 502; 1978. (no refs)

- 78-1284 **Identification of the Principal Aflatoxin B<sub>1</sub> DNA Adduct Formed In Vivo in Rat Liver (Meeting Abstract).** (Eng) Croy, R. G. (Massachusetts Institute of Technology, Cambridge, MA, 02139); Essigmann, J. M.; Reinhold, V. N.; Wogan, G. N. *Proc Am Assoc Cancer Res* 19: 191; 1978. (no refs)



285 **Hepatic Uptake and Disposition of Rubratoxin B (Meeting Abstract).** (Eng) Unger, P. D. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS, 39216); Hayes, A. W.; Mehen, H. M. *Fed Proc* 37(3): 261; 1978. (no refs)

286 **Induction of Hepatic Mixed Function Oxidases by Patulin in Male Mice (Meeting Abstract).** (Eng) Siraj, M. Y. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS, 39216); Hayes, A. W. *Fed Proc* 37(3): 320; 1978. (no refs)

287 **Dietary, Bacterial, and Host Genetic Interactions in the Pathogenesis of Transmissible Murine Colonic Hyperplasia.** (Eng) Barthold, S. W. (Section of Comparative Medicine, Yale Univ. Sch. Medicine, New Haven, CT 06510); Osbaldiston, G. W.; Jonas, A. M. *Lab Anim* 17(6): 938-945; 1977.

Effects of diet and host genetics on the pathogenesis of murine colonic hyperplasia induced by *Citrobacter freundii* (2-3 drops po in thioglycollate broth) were investigated. Commercial laboratory diets had significantly different effects on the severity of hyperplasia in *C. freundii*-inoculated C57BL/6J, DBA/2J, C3H/HeJ, and NIH Swiss mice. The diet also affected colonic crypt height in uninoculated controls, but the dietary constituents responsible for these effects were not determined. The severity of the colonic lesions varied with host strain, the degree of hyperplasia being greatest in NIH Swiss mice and least severe in C57BL/6J and DBA/2J mice. Neither F344 rats nor Syrian hamsters developed colonic hyperplasia after exposure to *C. freundii* 4280. Of 20 *C. freundii* isolates, only the 4280 variant was able to infect and produce colonic hyperplasia in susceptible mice. (7 refs.)

288 **Carcinogenicity of Some Folk Medicinal Herbs in Rats.** (Eng) Kapadia, G. J. (Dept. Biomedical Chemistry, Coll. Pharmacy and Pharmacal Sciences, Howland Univ., Washington, DC 20059); Chung, E. B.; Ghosh, S.; Shukla, Y. N.; Basak, S. P.; Morton, J. F.; Pradhan, S. *J Natl Cancer Inst* 60(3): 683-686; 1978.

289 **Plant materials tested for carcinogenicity in outbred albino rats.** 12 plant materials tested for carcinogenicity in outbred albino rats, 5 induced malignant mesenchymal tumors after oral administration for up to 78 wk. Extracts of the tannin-rich plants *Areca catechu* and *Rhus copallina* produced tumors in 100% and 30%, respectively, of the mice. Among plants not rich in tannin, *Sassafras albidum*, *Diospyros virginiana*, and *Chenopodium ambrosioides* were tumorigenic in > 60% of the treated animals. (22 refs.)

78-1289 **Carcinogenesis in the Syrian Golden Hamster by N-Methyl-N-formylhydrazine (MFH) of the False Morel Mushroom (Meeting Abstract).** (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska, Omaha, NB, 68105); Nagel, D. *Fed Proc* 37(3): 231; 1978. (no refs)

78-1290 **Influence of Cabbage in the Diet on Chemically Induced Tumors in Inbred Mice (Meeting Abstract).** (Eng) Hendricks, D. G. (Dept. Nutrition and Food Sciences, Utah State Univ., Logan, UT, 84322); Srisangnam, C.; Salunkhe, D. K.; Mahoney, A. W. *Fed Proc* 37(3): 357; 1978. (no refs)

78-1291 **Effect of 1,2-Dimethylhydrazine on RNA, DNA, and Protein Formation of Colon Mucosal Cells of Rats (Meeting Abstract).** (Eng) Bradac, C. J. (West Virginia Univ., Morgantown, WV, 26506); Watne, A. L.; Lai, H. Y. *Fed Proc* 37(3): 450; 1978. (no refs)

78-1292 **Induction of DNA Repair and Suppression of DNA Synthesis by Carcinogens in Colon Organ Culture (Meeting Abstract).** (Eng) Reiss, B. (Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595); Williams, G. M. *Fed Proc* 37(3): 749; 1978. (no refs)

78-1293 **Protein Source and Colon Carcinogenesis (Meeting Abstract).** (Eng) Vissek, W. J. (Univ. Illinois, Urbana, IL, 61801); Clinton, S. K.; Destree, R.; Anderson, D. B.; Truex, C. R.; Imrey, P. B. *Fed Proc* 37(3): 262; 1978. (no refs)

78-1294 **Analgesic Nephropathy Complicated by Development of Transitional Cell Carcinoma of the Renal Pelvis and Ureter.** (Eng) Kench, P. (Sch. Pathology, Univ. New South Wales, P. O. Box 1, Kensington, New South Wales 2033, Australia). *Med J Aust* 2: 607-610; 1977.

A 67-yr-old woman with analgesic nephropathy and papillary necrosis, calcification, and osseous metaplasia developed transitional cell carcinoma of the renal pelvis and ureter. Based on this case and seven in the literature, it is suggested that analgesics containing phenacetin may play an etiological role. (16 refs)



- 78-1295 The Influence of N-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide and Phenacetin on the Immune Status in Male Fischer Rats.** (Eng) Johansson, S. (Dept. Pathology, Univ. Goteborg, Goteborg, Sweden); Cohen, S. M.; Yang, J. P. S.; Arai, M.; Friedell, G. H. *Invest Urol* 15(4): 308-311; 1978.

The effect of N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) and phenacetin on the immune status of Fischer rats was determined by spleen plaque and phytohemagglutinin blastogenesis assays 6, 10, and 15 wk after the rats were fed a diet containing 0.2% and 0.535%, respectively, of the test chemicals. Comparisons were made with a negative control group and with a group fed azathioprine (0.02% of the diet), a known immunosuppressive chemical. FANFT showed no suppressive effects on either the humoral or the cellular immune response. Although only of borderline significance, FANFT actually appeared to augment immune responses by 15 wk of feeding. The urinary bladder of rats given FANFT exhibited mild to moderate focal hyperplasia after 6 wk, marked hyperplasia after 10 wk that progressed to carcinoma even if FANFT was removed from the diet, and marked hyperplasia with papillary and nodular lesions at 15 wk. No histological evidence of urothelial damage was present by the end of 15 wk of feeding phenacetin, but there were changes of slight to borderline significance in the immune response. The humoral response went from a slight depression at 6 wk, to normal at 10 wk, to slightly increased at 15 wk. Azathioprine suppressed both the humoral and cellular immune response at all time periods. The results indicate that immunosuppression is not necessary for the development of FANFT-induced noninvasive carcinoma of the urinary bladder in Fischer rats. (33 refs)

- 78-1296 The Effects of Nitrofurantoin Derivatives on Hepatic Microsomal Mixed-Function Oxidase Activity in Rats.** (Eng) Fukuhara, M. (Inst. Public Health, 6-1, Shirokanedai 4 chome, Minato-ku, Tokyo, 108, Japan); Takabatake, E. *Toxicol Appl Pharmacol* 42(3): 571-581; 1977.

The effects of four nitrofurantoin derivatives, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (furylfuramide), 2-amino-5-[1-(2-furyl)-2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole (furazolidone), 5-nitro-2-furfurylidene-3-amino-2-oxazolidone (furazolidone), and bis(5-nitrofurfurylidene)acetone guanyldihydrochloride (panazon), on mixed-function oxidase activity were studied in rat hepatic microsomes. Dietary administration (0.03%-0.3%) of the compounds for 7 days to Wistar male rats produced varying degrees of liver enlargement. Furylfuramide was most potent in increasing liver wt and in reducing the microsomal enzyme activity. In rats fed a 0.1% furylfuramide-containing diet, cytochrome P-450 concentration and the activity of aminopyrine N-demethylase and aniline hydroxylase were markedly reduced during the 29-day experimental period; cytochrome B<sub>5</sub> concentration and the activity of NADPH-cytochrome c reductase were reduced

also, but to a lesser degree. Dietary administration of furylfuramide to pentobarbital or 3-methylcholanthrene pretreated rats resulted in an increase in liver wt and a decrease in microsomal enzyme activity. The pentobarbital sleeping time was prolonged by 57% in rats fed a 0.1% furylfuramide diet for 7 days, suggesting that the compound is an inhibitor of pentobarbital metabolism. Furylfuramide depressed the activity of some of these oxidases in vitro. The results suggest that hepatic injury or dysfunction can result from exposure to furylfuramide, since established hepatocarcinogens are found among the microsomal drug metabolite depressing agents. (19 refs.)

- 78-1297 Chronic Toxicity of 2-(2-Furyl)-3-(5-Nitro-2-furyl)acrylamide (AF-2) in Mice, with Special Reference to Carcinogenicity in the Forestomach.** (Eng) Yokoro, K. (Dept. Pathology, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima 734, Japan); Kajihara, H.; Kodama, Y.; Nagao, K.; Hamada, K.; Kinomura, A. *Gann* 68(6): 825-828; 1977.

The chronic toxicity of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), which had been widely used in Japan as a food additive, was studied in ICR/JCL mice of both sexes fed a diet containing 0.4% or 0.08% AF-2. More than 70% of mice fed the higher dose developed forestomach tumors, the majority of which were squamous cell carcinomas with metastatic foci. Fewer tumors occurred in the low dose group, and the latent period was longer. The major lesions were single papillomas. Eleven cases of leukemia developed in AF-2-treated females, compared with 2 in the control females. Nonneoplastic liver and kidney lesions and amyloidosis of various organs was also observed in some 2-fed mice. (19 refs)

- 78-1298 Model Building and Extended Huckel Calculations in the Prediction of Reactions of Chemical Carcinogens (Meeting Abstract).** (Eng) Scribner, J. D. (Pacific Northwest Res. Foundation, 1102 Columbia St., Seattle, WA, 98104); Fisk, S. R. *Proc Am Assoc Cancer Res* 19: 1978. (no refs)

- 78-1299 The State of Ribosomal Protein Phosphorylation During Thioacetamide-induced Liver Injury.** (Eng) Gressner, A. M. (Dept. Clinical Chemistry, Medical Faculty RWTH, Aachen, W. Germany); Greil, H. *Exp Mol Pathol* 28(1): 39-47; 1978.

Ribosomal protein phosphorylation during thioacetamide (TAA)-induced liver injury was investigated in male Sprague-Dawley rats.



Wiley rats inoculated ip with 100 mg/kg TAA. One to 48 hr after TAA treatment, the rats were injected ip with  $^{32}\text{P}$ -phosphoric acid and sacrificed 30 min later. Radioactivity associated with the 80S ribosomes was enhanced 2.6-fold after TAA treatment. Ribosomal subunits free of extraneous proteins were then prepared. At 3 and 6 hr after the onset of injury, phosphorylation of the 40S subunit was stimulated 9 and 9 times and phosphate incorporation into the 40S ribosomal proteins was stimulated 3.5 and 6 times, respectively. The specific radioactivity of the 60S subunit protein was not significantly changed by TAA treatment. Gel electrophoresis of 40S subunit proteins indicated that only the S6 protein was affected by treatment. During liver damage, the phosphorylation of this protein was stimulated more than eightfold 3 and 6 hr after TAA treatment. Two days after treatment, a tendency toward regeneration of the normal S6 protein was observed. (40 refs)

**78-1300 Inhibitory Action of Chemical Carcinogens on Deoxyribonucleic Acid Replication by Cultured HeLa Cells (Meeting Abstract).** (Eng) Warren, J. R. (Dept. of Pathology, Northwestern Univ. Medical Sch., Chicago, IL, 60611). *Fed Proc* 37(3): 451; 1978. (no refs)

**78-1301 Role of Arylhydroxamic Acid Acyltransferase in the Mutagenicity of N-Hydroxy-N-2-Fluorenylacetylamide in *Salmonella typhimurium*.** (Eng) Weeks, C. E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Allaben, W. T.; Louie, S. C.; Lazear, E. King, C. M. *Cancer Res* 38(3): 613-618; 1978.

The role of arylhydroxamic acid acyltransferase in the mutagenicity of N-hydroxy-N-2-fluorenylacetylamide (N-hydroxy-FAA) was investigated in the *Salmonella typhimurium* strain mutagenicity assay system, and the possible relationship between mutagenicity and nucleic acid adduct formation was evaluated. *Salmonella* strain TA1538 was used as the indicator strain. Partially purified acyltransferase greatly enhanced the mutagenicity of N-hydroxy-FAA. Further purification by ion-exchange chromatography followed by gel permeation chromatography yielded acyltransferase preparations that retained mutagenic activation potential. N-Fluorenylacetylamine, which competes for the acyl group during intramolecular N'-O acyl transfer, or guanosine monophosphate, which competes with nucleic acid for the reactive electrophile generated from N-hydroxy-FAA by acyltransferase, decreased the acyltransferase-catalyzed nucleic acid:fluorenylacetylamine adduct formation by 90% and 70%, respectively. When strain TA1538 was incubated with N-2-fluorenylacetylamide, S-9 fraction (mouse liver supernatant fraction from centrifugation at 9,000 x g), and various amounts of transfer RNA (tRNA) in the external media, the tRNA (up to 10 mg/plate) had no effect on N-2-

fluorenylacetylamide mutagenicity. It is concluded that (1) strain TA1538 does not detect the reactive electrophile, N-acetoxy-N-2-fluorenylacetylamine, formed extracellularly from N-hydroxy-FAA by N'-O acyl transfer; (2) a metabolite of N-hydroxy-FAA that is not capable of spontaneous covalent reaction with nucleic acids is generated by acyltransferase and is responsible for induction of mutations, and (c) bacterial activation pathways may play a role in mutations produced by arylamine derivatives. (36 refs)

**78-1302 An Improved Method for DNA Alkaline Gradient Analysis and its Application to the Effect of Carcinogens on Mouse Liver DNA.** (Eng) Szafarz, D. (Fondation Curie-Institut du Radium, 91405 Orsay, France). *Biochimie* 59(10): 775-778; 1977.

An alkaline sodium iodide density gradient technique was used in sedimentation rate centrifugation studies of the in vivo induction of single-strand breaks (SSB) in DNA. The technique was applied to the study of SSB induction in mouse liver DNA by known carcinogens. The combination of this type of gradient with a sensitive fluorometric method to estimate the DNA makes it possible to analyze very small amounts of DNA without the need for labeling the nucleic acid with radioactive thymidine. The effect of N-hydroxy-N-acetylaminofluorene (N-OH-AAF: 1 mg ip) on the structure of XVII nc/Z strain mouse liver DNA was studied at various intervals postinjection. At 2 hr after injection, the DNA peak was at the same position as that of control liver DNA, indicating that no SSB had yet appeared; at 16 hr, the peak had shifted to a more slowly sedimenting position, as a result of an increase in SSB. Repair was detected at 24 hr, and this process had progressed at 48 hr. Four hours after an ip injection of diethylnitrosamine (10 mg/kg), many SSB were demonstrated. The results show that this method is useful in the study of SSB in vivo, and it is sensitive enough to allow the analysis of small amounts of DNA compatible with alkaline gradient centrifugation. In addition, the low viscosity and density range of the gradient also allow the separation of relatively large pieces of DNA. (31 refs)

**78-1303 Activation of the Carcinogen N-Hydroxy-2-Acetylaminofluorene by Rat Mammary Peroxidase.** (Eng) Reigh, D. L. (Biomembrane Res. Lab., 825 Northeast 13th St., Oklahoma Medical Res. Foundation, Oklahoma City, OK, 73104); Stuart, M.; Floyd, R. A. *Experientia* 15(1): 107-108; 1978.

A peroxidase preparation from rat mammary gland parenchymal cells, a target tissue of arylamine carcinogens, activated the carcinogen N-hydroxy-2-acetylaminofluorene via a nitroxyl free-radical intermediate to the more active carcinogens nitrosofluorene and N-acetoxy-2-



acetylaminofluorene, according to electron spin resonance data and thin-layer chromatography. Hydrogen peroxide, cumene hydroperoxide, and linoleic acid hydroperoxide were effective as substrates. The antioxidants ascorbate, propyl gallate, and reduced glutathione prevented the free-radical activation route. (10 refs)

**78-1304 Studies on Carcinogen-Chromatin Interactions (Meeting Abstract).** (Eng) Schwartz, E. L. (Dept. Pharmacology, Michigan State Univ., East Lansing, MI, 48824); Goodman, J. I. *Fed Proc* 37(3): 749; 1978. (no refs)

**78-1305 The Ultrastructure of Carcinogen-induced Altered Hepatocellular Foci Identified by Their Resistance to Iron Accumulation in Siderotic Livers (Meeting Abstract).** (Eng) Hirota, N. (Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595); Williams, G. M. *Fed Proc* 37(3): 597; 1978. (no refs)

**78-1306 Effect of Dietary Lipids on the Metabolic Activation of a Carcinogenic Pesticide (Meeting Abstract).** (Eng) Fann, D. (Texas Tech Univ., Lubbock, TX, 79409); Felkner, I. C.; Yang, S. P.; Sproat, H. F. *Fed Proc* 37(3): 262; 1978. (1 ref)

**78-1307 Feedback Control of Cholesterol Biosynthesis in Rats and Mice Fed the Carcinogens Benzo(a)pyrene and 2-Acetylaminofluorene (AAF) (Meeting Abstract).** (Eng) DePass, L. R. (Univ. Arkansas Medical Sciences, Little Rock, AR, 72201); Morris, M. D. *Proc Am Assoc Cancer Res* 19: 237; 1978. (no refs)

**78-1308 Trace Analysis of 3,3'-Dichlorobenzidine in Animal Chow, Wastewater and Human Urine by Three Gas Chromatographic Procedures.** (Eng) Bowman, M. C. (Dept. Health, Education, and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR, 72079); Rushing, L. G. *Arch Environ Contam Toxicol* 6(4): 471-482; 1977.

Three gas chromatographic procedures for analyzing trace amounts of 3,3'-dichlorobenzidine and its dihydrochloride salt in animal chow, waste water, and human urine are described. With the use of spiked samples of these compounds,

the respective minimal detectable residues were approx 3, 18 parts per trillion (ppt), and 60 ppt. (15 refs)

**78-1309 Enhanced Survival of Ultraviolet-irradiated Herpes Simplex Virus in Carcinogen-pretreated Cells.** (Eng) Lytle, C. D. (Dept. Health, Education and Welfare, Bureau Radiological Health Food and Drug Admin., 5600 Fishers Lane, Rockville, MD, 20857); Coppey, J. *Nature* 272(5648): 60-62; 1978.

A study was conducted to determine whether treatment of CV-1 monkey kidney cells with carcinogens would result in enhanced survival of UV-inactivated herpes simplex virus (HSV). The CV-1 cells were treated with various concentrations of aflatoxin B<sub>1</sub>, acetylaminofluorene (AAF), n-acetylaminofluorene (n-acetoxy-2-AAF), or n-hydroxyacetylaminofluorene (n-hydroxy-2-AAF) and then infected with UV-irradiated or unirradiated HSV. Enhanced reactivation was determined by calculating the reactivation fraction (RF), the ratio of the surviving fraction of the virus in treated cells to that in untreated cells. The RF was increased to values of 2-4 in cells treated with aflatoxin B<sub>1</sub>, n-acetoxy-2-AAF and n-hydroxy-2-AAF, but it remained at 1 in AAF-treated cells. In all cell treatments, the RF increased with delay of infection for 24-36 hr, then decreased. The enhanced reactivation system of HSV and CV-1 cells could be used as a screening system for testing the carcinogenic potential of chemical compounds in mammalian cells. The sensitivity (nanogram of aflatoxin B<sub>1</sub>) and the short assay time (3 d) are advantages over other mammalian systems. (22 refs)

**78-1310 A Comparison of the Changes Induced in Liver by Feeding Low Levels of Aflatoxin B<sub>1</sub> or an Azo Dye.** (Eng) Neal, G. E. (MRC Toxicology Unit, Medical Res. Council Labs., Carshalton, Surrey SM5 4EF, England); Butler, W. H. *Br J Cancer* 37(1): 55-60; 1978.

Changes occurring in liver nuclear populations of male Fisher rats while they were being fed low dietary levels of aflatoxin B<sub>1</sub> (4 ppm) or 2-methyl-4-dimethylaminoazobenzene (Me-DAB: 0.04%) for 6 wk were monitored by histological examination and zonal rotor centrifugation at weekly intervals. Following an initial period showing little change, a reduction of most of the tetraploid hepatocyte population and massive tissue necrosis occurred between 3-4 wk feeding with either carcinogen. A compensatory proliferation of predominantly diploid hepatocytes took place in the presence of a continuing supply of either carcinogen, indicating that not only does feeding each carcinogen induce the production of a population of hepatocytes resistant to the cytotoxicity of the inducing agent, but that these hepatocytes are also resistant to other carcinogen. These findings demonstrate that a feeding period longer than 3 wk is necessary to induce hepatic



as with low levels of 2-Me-DAB or aflatoxin B<sub>1</sub>. They indicate that the time course and nature of the changes in the livers of male Fischer rats induced by this feeding schedule are similar for 2-Me-DAB and aflatoxin B<sub>1</sub>. (9 refs)

- 811 Acute Effects of Selected Hepatocarcinogens on Polyribosomes and Protein Synthesis in the Liver of Rats Fed Purified Diets Containing Hepatocarcinogens.** (Eng) Sidransky, H. (Dept. Pathology, Univ. South Florida, Coll. Medicine, Tampa, FL, 33620); Verney, E. *Cancer Res* 38(4): 1166-1172; 1978.

The acute effects of various carcinogens on hepatic polyribosomes and protein synthesis were studied in female Sprague-Dawley rats fed (1) ad libitum, for 3-29 wk, purified diets containing 0.025% N-2-fluorenylacetamide (2-FAA) or 0.032% 3'-methyl-4-dimethylaminoazobenzene (Me-DAB) or (2) force-feeding, for 3 days, purified diets containing 2-Me-DAB, dimethylnitrosamine (DMN: 0.8 mg/100 g, daily feeding only), 0.032% thioacetamide (TA), or 0.032% L-ethionine. All animals then received ip injections of L-ethionine (100 mg/100 g 4 hr before death), DMN (0.8 mg/100 g 14 hr before death), TA (5 mg/100 g 4 hr before death), or aflatoxin B<sub>1</sub> (AFB: 0.6 mg/100 g 12 hr before death). The long-term feeding of 2-FAA or Me-DAB diminished the acute toxic effects of ethionine, disaggregation of polyribosomes, and inhibition of protein synthesis in the liver. Conversely, force-feeding of 2-FAA, Me-DAB, DMN, TA, or L-ethionine diminished the acute toxic effects of ethionine on hepatic polyribosomes and protein synthesis. Rats force-fed with the diets and then challenged acutely with TA, DMN, or AFB had variable responses of hepatic polyribosomes and protein synthesis. (34 refs)

- 812 Respiration of Cells and Isolated Mitochondria of Rat Liver During Early Stages of Carcinogenesis.** (Rus) Koblyakov, V. A. (Lab. Chemical Carcinogenesis, Cancer Res. Center, Moscow, USSR); Ryabikh, T. *Russk. Onkol* 23(11): 70-75; 1977.

Long-bred albino rats were fed the carcinogens 3'-methyl-4-dimethylaminoazobenzene (3'-MDAB: 0.6 g/kg of food, for 3 wk) or acetylaminofluorene (doses as above, for 3 wk), followed by a 10-day interval and then again for 3 wk), or the noncarcinogenic analog 2-MDAB. The respiration index of isolated mitochondria from carcinogen-exposed rats did not differ from that in the mitochondria of rats fed 2-MDAB or control (untreated) rats. It was suggested that the metabolites of the carcinogens form unstable bonds with the mitochondrial membranes that cannot be detected in vitro. (10 refs)

- 813 A Possible Role for Glutathione (GSH) in the Hepato-Biliary Fate of Dimethylaminoazoben-**

**zene (DAB) in the Rat (Meeting Abstract).** (Eng) Levine, W. G. (Dept. Molecular Pharmacology, Albert Einstein Coll. of Medicine, Bronx, NY, 10461); Finkelstein, T. T.; Opler, A.; Israel, D. *Fed Proc* 37(3): 465; 1978. (no refs)

- 78-1314 Synthesis and Accumulation of Polyamines in Rat Liver During Chemical Carcinogenesis.** (Eng) Scalabrino, G. (Istituto di Patologia Generale, Università Degli Studi, 20133 Milan, Italy); Poso, H.; Holtta, E.; Hannonen, P.; Kallio, A.; Janne, J. *Int J Cancer* 21(2): 239-245; 1978.

Sprague-Dawley rats were given a diet containing 0.06% 4-dimethylaminoazobenzene for 6 mo, and the activity of several enzymes, polyamine concentrations, and liver morphology were examined at monthly intervals. After 1 mo of feeding, L-ornithine decarboxylase (OD) activity was six times higher than that of controls and S-adenosyl-L-methionine decarboxylase (AMD) activity two times higher. These values returned to near normal within the next 2 mo, but 4 mo after the start of the azo-dye diet, both enzyme activities rose again and remained high until liver tumors appeared (6 mo). The biphasic response of the two decarboxylases was specific to the liver. The concentration of putrescine in the liver followed the fluctuations of OD activity. Spermidine and spermine concentrations were normal, although the activities of spermidine synthase and spermine synthase were lower in animals fed the carcinogenic diet than in controls. The striking response of OD to porcine growth hormone was reduced markedly, and the moderate stimulation elicited by glucagon completely disappeared during the carcinogenic diet. The response of AMD to growth hormone remained unchanged, but the marginal stimulation evoked by either glucagon or hydrocortisone in normal rats disappeared completely after 4 mo of dye feeding. The results indicate that the activities of OD and AMD are greatly enhanced several months before the appearance of visible tumor in the liver. (41 refs)

- 78-1315 The Effect of Selenium on Peripheral Blood Lymphocytes in Rats Chronically Exposed to Benzene.** (Pol) Aleksandrowicz, J. (Kliniki Hematologicznej, Instytutu Medycyny Wewnętrznej AM, skr. poczt. 13, 30-969 Krakow, Poland); Starek, A.; Moszczynski, P. *Med Pr* 28(6): 453-459; 1977.

The influence of selenium (1 or 5 µg/kg/day x 10 gastric intubation) on the hematological changes induced by benzene vapor (1,200 mg/m<sup>3</sup>, 6 hr/day for 12 wk) was studied in adult male Wistar rats. Twelve control animals were exposed to benzene only; the experimental animals received 1 (10 rats) or 5 (7 rats) µg/kg selenium in the form of sodium selenate prior to benzene exposure. The hematological status was determined before the experiment and after 6 and 12 wk of exposure to benzene. Lymphocytopenia, which correlated with the duration of benzene exposure, and thrombocyto-



penia were found in the control rats and in the animals pretreated with 1  $\mu\text{g/kg}$  of selenium. The rats pretreated with 5  $\mu\text{g/kg}$  of selenium failed to develop lymphocytopenia, and they developed thrombocytopenia only at the end of the exposure. A significant increase in the reticulocyte count was seen in this group and in the controls. The findings indicate that at a dose of 5  $\mu\text{g/kg}$ , selenium protects the lymphocytes from the toxic effects of benzene. (23 refs)

- 78-1316 Mutagenicity in *Salmonella typhimurium* Mutants of the Benzene-soluble Organic Matter Derived from Air-borne Particulate Matter and Its Five Fractions.** (Eng) Teranishi, K. (Public Health Inst. Hyogo Prefecture, 2-1 Arata-cho, Hyogo-ku, Kobe 652, Japan); Hamada, K.; Watanabe, H. *Mutat Res* 56(3): 273-280; 1978.

The mutagenicity of benzene-soluble airborne particulate matter was examined using *Salmonella typhimurium* mutants TA100, TA98, TA1535, TA1536, TA1537, and TA1538. The benzene-soluble material was separated into acidic, basic, aliphatic, polyaromatic, and oxygenated fractions and examined for mutagenicity with and without the S-9 fraction from the livers of phenobarbital- or dibenz(a,h)anthracene-treated Sprague-Dawley JCL rats. The benzene-soluble organic matter (tar) was not mutagenic with TA1535 and TA1536, even in the presence of the S-9 fraction. With TA1537, TA1538, TA98, and TA100, however, the tar was mutagenic in the presence and absence of the S-9 fraction. With TA98, linear dose-response curves were obtained for the tar and the acidic, polyaromatic, and oxygenated fractions in the presence of the S-9 mix. However, the S-9 mix was not necessary for activation of the acidic fraction or the tar. Among the five fractions tested, the acidic, polyaromatic, and oxygenated fractions played an important role in the mutagenicity of the tar derived from airborne particulate matter. (15 refs)

- 78-1317 Benzene in Consumer Products (Letter to Editor).** (Eng) Young, R. J. (Natl. Inst. Occupational Safety and Health, Center Disease Control, 4676 Columbia Parkway, Cincinnati, OH, 45226); Rinsky, R. A.; Infante, P. F.; Wagoner, J. K. *Science* 199(4326): 248; 1978.

The amount of benzene exposure associated with the use of benzene-containing paint stripper was analyzed in an 8- x 21- x 20-ft room. During the 30-min procedure, airborne concentrations ranged from 73 to 225 ppm, values clearly in excess of the proposed standard of 1 ppm. Because of the high benzene concentrations in several commercial products, individuals should protect themselves until regulatory activation is taken. (10 refs)

- 78-1318 Immunologic Manipulation of DNBA Carcinogenesis in the Hamster Cheek Pouch by DNCB**

**Contact Hypersensitivity (Meeting Abstract).** (Eng) Mohammad, A. R. (Univ. Tennessee Coll. Dentistry, Memphis, TN, 38163); Mincer, H. H. *J Dent Res* 57(A): 234; 1978. (no refs)

- 78-1319 Subacute Toxicity of 1,2,4-Trichlorobenzene (TCB) in Sub-Human Primates (Meeting Abstract).** (Eng) Smith, C. C. (Dept. Environmental Health Univ. Cincinnati, Coll. Medicine, Cincinnati, OH, 45269); Cragg, S. T.; Wolfe, G. F. *Fed Proc* 37(3): 248; 1978. (no refs)

- 78-1320 Effects of Microsomal Stimulators on the In Vitro Metabolism of 2,5,2',5'-Tetrachlorobiphenyl (TCB), a Component of Carcinogenic Polychlorinated Biphenyl Mixtures (Meeting Abstract).** (Eng) Preston, B. (Univ. Wisconsin, Madison, WI, 53706); Seymour, J. Kordes, J.; Hsia, M. T.; Allen, J. R. *Proc Am Assoc Cancer Res* 19: 200; 1978. (no refs)

- 78-1321 Mutagenicity Testing of Certified Food Colors and Related Azo, Xanthene and Triphenylmethane Dyes with the *Salmonella*/Microsome System.** (Eng) Brown, J. P. (Dynapol, 1454 Page Mill Road, Palo Alto, CA 94304); Roehm, G. W.; Brown, R. J. *Mutat Res* 56(3): 271; 1978.

A total of 37 azo, xanthene, and triphenylmethane dyes, including FD and C colors currently approved for use in US and a number of delisted food colors, were tested for mutagenicity in the *Salmonella typhimurium* system using strains TA1535, TA100, TA1537, TA1538, and TA98. 15 azo dyes were also assayed after chemical reduction to their component amines. Several azo dyes were subjected to liquid and plate tests involving initial 16-hr anaerobic incubation to facilitate microbial reduction of the azo bond. None of the presently listed FD and C colors was mutagenic in any of the test modifications. Among the formerly listed colors, Orange Butter Yellow (p-dimethylaminoazobenzene), a recognized animal carcinogen, was mutagenic in the aerobic liquid test. Acid Alizarin Yellow R and Alizarin Yellow GC were directly mutagenic, Acid Alizarin Red B and Methyl Red required microsomal activation, and Acid Alizarin Violet N and Sudan IV required chemical reduction and microsomal activation. Of the nonazo dyes tested, only 9-(2-sulfophenyl)-1-hydroxy-3-isoxanthone and its 2,4,5,7-tetrabromo derivative were mutagenic. (26 refs)

- 78-1322 Duration of Mitotic Cycle in Mouse Liver Cells at Different Stages of o-Aminoazotoluene-induced Carcinogenesis.** (Rus) Mustafin, A. G. (Dept. Biochemistry, Moscow Univ., Moscow, USSR)



Second N. I. Pirogov Medical Inst., Moscow, USSR). *Il Eksp Biol Med* 85(1): 61-64; 1977.

duration of various phases of the mitotic cycle was assessed autoradiographically in the hepatocytes of random albino rats with o-aminoazotoluene-induced adenomas and hepatomas. The duration of the S phase in the hepatoma cells (12.8 hr) was slightly shorter than that in normal hepatocytes (13.8 hr) or in adenomatous nodes (13.9 hr), but duration of G<sub>2</sub> + 1/2M phase (2.2 hr) was almost the same as that in normal hepatocytes. (13 refs.)

### 1323 Non-carcinogenicity of Hair Dyes: Lifetime Percutaneous Applications in Mice and Rabbits.

(Eng) Stenback, F. G. (Dept. Pathology, Kajaanintie 52 D, SF-920220 Oulu 22, Finland); Rowland, J. C.; Sell, L. A. *Food Cosmet Toxicol* 15(6): 601-606; 1977.

Three hair-dye components, p-amino-o-nitrophenol, p-phenylenediamine, or sodium thioglycollate (0.02 ml, 2x/wk acetone soln), were applied topically to the shaved interdigital skin of female Swiss mice (7 wk old) and to the inside of the ear of female rabbits (8 wk old). The mice were treated for their natural life-spans (up to 130 wk), and the rabbits were treated until sacrificed at 85 wk. Neither species showed significant change in body wt gain, behavior, appearance, food intake. The life-span of the mice was unaffected. No abnormalities of blood or urine were observed in the rabbits. The treated mice had tumors of other organs (lymphomas; benign pulmonary adenomas; hemangiomas of the liver, lung, subcutis; and ovarian tumors), most of which were benign, but the frequency was no greater than that in untreated controls. None of the treated animals had grossly visible dermal tumors. Mice from all treatment groups had a few benign dermatofibromas, but none of the chemicals induced epidermal hyperplasia. These compounds did not cause local changes in the rabbits; p-phenylenediamine can cause contact sensitization in man, but there was no evidence of carcinogenicity in the rabbits. No neoplasms were observed in rabbits. The positive control groups of both mice and rabbits (treated with low doses of 7,12-dimethylbenz(a)anthracene) developed large numbers of skin tumors, which confirmed the sensitivity of these models for carcinogenesis studies. (26 refs)

### 1324 Mutagenicity and Chromosomal Aberrations as an Analytical Tool for In Vitro Detection of Mammalian Enzyme-mediated Formation of Reactive Metabolites.

(Eng) Greim, H. (Abteilung Toxikologie, Gesellschaft für Strahlen- und Umweltforschung München, Institut für Landstrasse 1, D-8042 Neuherberg, W. Germany); Boes, D.; Egert, G.; Goggelmann, W.; Kramer, M. *Arch Toxicol (Berl)* 39(1/2): 159-169; 1977.

The mutagenic activity of various chemicals was tested in

bacterial and mammalian assay systems. Trichloroethylene, 1,1-dichloroethylene, vinyl chloride, tetrachlorocyclopentadiene, and the nitroso derivatives of the pesticides Carbaryl, Prometryn, and Dodin were mutagenic to *Escherichia coli* K12 and/or *Salmonella typhimurium* in the presence of metabolically active mouse liver microsomes. Under the same conditions, tetrachloroethylene, 1,2-cis- and trans-dichloroethylene, hexachlorocyclopentadiene, carbon tetrachloride, chloroform, halothane, trichlorofluoromethane, and styrene were not activated to mutagenic species. Incubation of human lymphocytes with dimethylnitrosamine in the presence of mouse liver microsomes induced chromosomal aberrations: there was a significantly increased number of gaps, but crossovers or translocations and breaks were less frequent. It is concluded that human lymphocytes can be successfully used in metabolizing test systems in combination with mouse liver microsomes to activate potential mutagens. (60 refs)

### 78-1325 Some Observations on the Determination of Monomer Residues in Foods. (Eng) Chudy, J.

C. (Dept. Industry, Lab. Government Chemist, London SE1 9NQ, England); Crosby, N. T. *Food Cosmet Toxicol* 15(6): 547-551; 1977.

Parameters that might affect the headspace gas chromatographic (HSGC) determination of vinyl chloride (VC) and acrylonitrile (AN) residues in foods were investigated. They included solvent type, monomer distribution between the headspace and the liquid, and storage duration and temperature. Samples of orange drink, wine, olive oil, and water, which previously had not been in contact with polyvinyl chloride (PVC), were poured into PVC bottles so that a minimum air space was left above the liquid and then sealed. At monthly intervals, 5-ml portions were removed and analyzed by HSGC. For VC, equilibrium was attained more rapidly in methyl ethyl ketone (MEK) than in water. At 30°C, full equilibrium was attained only after 2 hr; at 40°C, the equilibrium time was as short as 30 min. At 30°C, VC was 10 times more soluble in MEK than in water. After equilibrium was attained, the VC content of the headspace was stable for at least 5 hr. For AN, equilibrium was achieved in < 30 min in water or dimethylformamide and at 60 or 80°C, and little change was observed over 7 hr. When dimethylacetamide and a storage temperature of 80°C were used, however, the AN concentration in the headspace fell rapidly for 2 hr, beginning 1 hr after equilibrium was reached. The reason for this is not clear. The concentration of VC in the headspace gases at different headspace volumes rose markedly at volumes > 18 ml. There was a clear distinction between the aqueous and organic solvent systems, a fact that may be important in the design of a standard method for the analysis of VC in foods. Migration of VC from the container into the fluids increased during the first 3 mo, followed by a leveling off and, in some cases, a slow decay. When the same four fluids, to which varying wts of VC had been added, were kept in open glass jars, the VC content fell to half its original value within 2-4 hr. (9 refs)



- 78-1326 Pollution in Maryland Valley.** (Eng) Capurro, P. U. (Union Hosp. Cecil County, Elkton, MD, 21921). *Science* 199(4330): 731; 1978.

Since 1969, there has been an increase in lymphomas (9) within 4 kilometers of a chemical plant that began operation in 1961. The theory by a plant spokesman that the increase was due to an old paper mill that had operated at the same site from 1880 to 1948 is refuted based on the latency times for these tumors. (1 ref)

- 78-1327 Early Histological and Functional Alterations of Ethionine Liver Carcinogenesis in Rats Fed a Choline-deficient Diet.** (Eng) Shinozuka, H. (Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261); Lombardi, B.; Sell, S.; Iammarino, R. M. *Cancer Res* 38(4): 1092-1098; 1978.

The effects of feeding a choline-deficient (CD) or a choline-supplemented diet to male Sprague-Dawley rats on the early stages of DL-ethionine hepatocarcinogenesis were investigated. Rats were killed at various intervals, and the extent of fatty infiltration, cell necrosis, oval cell proliferation, and parenchymal cell mitoses was analyzed. Low levels of ethionine (0.05% and 0.10%), when fed with a CD diet, induced a massive proliferation of oval cells within 4 wk without significant cell necrosis or the presence of inflammatory cell infiltrates. The same levels of ethionine, when fed with a choline-supplemented diet, caused no significant histological alteration of the liver. In rats fed the CD + ethionine diet, there was a marked elevation in the content of  $\alpha_1$ -fetoprotein (AFP) in both the liver and plasma concomitant with the oval cell proliferation. Following immunofluorescence staining, the oval cells demonstrated intense staining for AFP and albumin. Hepatocytes stained only for albumin, and bile duct cells stained for neither AFP nor albumin. Significant elevations in total bilirubin occurred in rats fed the CD + ethionine diets for 2, 4, and 10 wk; these rats had no elevation in serum SGPT. These findings indicate that a diet deficient in choline markedly alters the response of rat liver to ethionine carcinogenesis. (42 refs)

- 78-1328 Cytogenetic Analysis of Mutagenic Activity of Repellents Dimethylphthalate and N, N-Diethylamide of Phenoxyacetic Acid.** (Rus) Yurchenko, V. V. (All-Union Scientific Res. Inst. Desinfection and Sterilization, Moscow, USSR). *Farmakol Toksikol* 40(4): 454-457; 1977.

The mutagenicity of two repellents, dimethyl phthalate (DMP) and the N,N-diethylamide of phenoxyacetic acid (P-203), was tested on random-bred albino mice. Two series of experiments were carried out. In the acute-exposure experiments, animals received a single ip injection of DMP (1,400 mg/kg) or P-203 (250 mg/kg); 18 hr later they were inoculat-

ed with colchicine and, 2 hr later, sacrificed. The bone marrow specimens showed a significant increase in the frequency of aberrant metaphases after exposure to P-203 (4.8%) compared with animals exposed to DMP (2.88%) or controls (1.88%). P-203 also increased the frequency of chromosome exchanges (ring fragments, isochromosome breaks and chromatid dicentric) to 25.0%, compared with 5.9% in controls and 0% in mice treated with DMP. In subacute-chronic-exposure experiments, mice received either a single topical application of a 50% alcohol solution of the repellent (1,250 mg/kg) or repeated daily applications (same dose, 1 wk for 1 mo). The animals were then subjected to partial hepatectomy; 28 hr later, they were sacrificed and the frequency and type of chromosome aberrations in the bone marrow specimens were studied. Single applications of DMP and P-203 did not increase the frequency of chromosome aberrations, but repeated applications had a pronounced mutagenic effect: the frequency of aberrant metaphases after DMP and P-203 was 7.50% and 7.66%, respectively, compared with 4.50% in controls. (6 refs)

- 78-1329 Mutagenic Effects of Chlorinated Phenoxyacetic Acids in *Drosophila melanogaster*.** (Eng) Magnusson, J. (Environmental Toxicology Unit, Wallenberg Lab., Lilla Frescati, S-104 05 Stockholm 50, Sweden); R. C.; Eriksson, A. *Hereditas* 87(1): 121-123; 1977.

The mutagenic effects of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-T butoxyethyl ester, dichlorophenoxyacetic acid (2,4-D), and 4-chlorophenoxyacetic acid (MCPA) in *Drosophila melanogaster* were investigated. 2,4,5-T (250 ppm) and MCPA (250 and 500 ppm) had no effect on nondisjunction, chromosome loss, and induced exchanges between X and Y. The number of recessive lethals was higher in 2,4-D- and 2,4,5-T-treated *Drosophila* than in their respective controls. These findings reached a significant level if the total material for the F<sub>2</sub> generations was combined. Furthermore, a significant increase of recessive lethals was obtained with 2,4-D in F<sub>1</sub> indicating that this compound gives rise to lethal mosaicism. (6 refs)

- 78-1330 Mutagenicity of Butadiene and Butadiene Monoxide.** (Eng) de Meester, C. (Lab. Analytical Chemistry, Sch. Pharmacy, Univ. Louvain, B-1200 Brussels, Belgium); Poncelet, F.; Roberfroid, M.; Mercier, M. *chem Biophys Res Commun* 80(2): 298-305; 1978.

Gaseous butadiene increased the number of his<sup>+</sup> *Salmonella typhimurium* TA1530 revertants/plate in the absence of liver Arochlor-induced S9 microsomal mix. In the presence of the mix, the mutagenic effect was dependent on its concentration. Butadiene monoxide produced histidine revertants without metabolic activation in TA1530, TA1535,



100. Butadiene monoxide could be a primary metabolite of butadiene. (25 refs)

1331 Propane Sultone: A Powerful Mutagen for Barley. (Eng) Singh, C. (Regional Res. Lab., Jamshedi, India); Kaul, B. L. *Mutat Res* 56(3): 355-368; 1978.

The mutagenic potential of propane sultone (PS), a potent mutagen, was assessed in barley. Fifty barley seeds were treated in three 4-hr treatments with 25 ml of 1, 2, or 3 mM PS. Root tips from the treated seeds were analyzed for chromosomal aberrations at the anaphase of the first mitotic division. 200 cells were analyzed for each treatment. Some of the seeds were planted to produce the M<sub>1</sub> generation. Seedling sterility, mitotic chromosomal aberrations, and M<sub>1</sub> spike sterility increased with increasing concentration of PS. At 20 C, 3.2%, 7.4% and 16.3% of the seedlings were injured by 1, 2, and 3 mM PS, respectively; at 30 C, these values were 0%, 4.7%, 15.8%, and 23.0%. At 20 C, 3%, 7%, 15%, and 25% of the cells were abnormal, and at 30 C, 4%, 13%, 18%, and 39% of the cells were abnormal, at the respective concentrations. M<sub>1</sub> spike sterility was 4.60, 14.58, 16.40, and 20.00 at 20 C, and 5.20, 16.0, 23.20, and 30.40 at 30 C, respectively. The overall frequency of M<sub>1</sub> spikes segregating chlorophyll-deficient mutations ranged from 8.0% to 10.0%, whereas the frequency of M<sub>2</sub> mutant seedlings ranged from 0.93% and 3.04%; the highest frequency for both was obtained with a treatment of 3 mM PS at 30 C. The results indicate that PS is a strong radiomimetic and mutagenic agent in barley, and, probably, a powerful mutagenic agent for higher plants. (14 refs)

1332 Changes in Transforming Activity of DNA Caused by Two Carcinogens Beta-naphthylamine and 1,3-Propanesultone (Meeting Abstract). (Eng) Kubinski, Z. O. (Univ. Wisconsin, Madison, WI, 53706); Kubinski, H. *Proc Am Assoc Cancer Res* 19: 227; 1978. (no refs)

1333 Carcinogenicity and Nephrotoxicity of 2-Amino-, 1-Amino-2-methyl-, and 2-Methyl-1-methoxyanthraquinone (Meeting Abstract). (Eng) Murthy, A. S. (Massachusetts Res. Inst., Worcester, MA, 01508); Russfield, A. B.; Miller, J.; Monson, R.; Weisburger, E. K. *Fed Proc* 37(3): 231; 1978. (no refs)

1334 Effect of Methylcobalamine on the Development of 3-Indolylacrylic Acid-induced Hemo-

blastoses. (Rus) Kudryavtsev, I. A. (Lab. Systemic Blood Diseases, Cancer Res. Center, Moscow, USSR); Golenko, O. D.; Myasishcheva, N. V. *Probl Gematol Pereliv Krovi* 23(3): 26-29; 1978.

The effect of methylcobalamine (MCA) on the development of 3-indolylacrylic acid (3-IAA)-induced hemoblastoses was studied in CC57 mice. The mice were divided into three groups. Group 1 received MCA (0.01 mg im, 2 x/wk, for 2.5 mo) and 3-IAA (2.5 mg sc, 2 x/wk, for 2.5 mo); Group 2 received 3-IAA alone; Group 3 served as untreated controls. MCA administration significantly enhanced the development of hemoblastoses. The hemoblastoses in Group 1 were first detected 9.5-10 mo after termination of treatment, compared with 12.5-13 mo in Group 2. The incidence of hemoblastoses was 31.25% in Group 1 and 11.11% in Group 2 (the incidence of spontaneous hemoblastoses in Group 3 was 6.67%). (15 refs)

78-1335 Presence of Glucuronated Metabolites of Safrole in the Urine of Treated Rats. (Fre) Levi, P. (Groupe de Recherche Differentiation biochimique de Cellules eucaryotes, Faculte de Medecine, Dijon, France); Jannaud, P.; Delaforge, M.; Morizot, J. P.; Maume, B. F.; Padiou, P. *C R Soc Biol (Paris)* 171(5): 1034-1040; 1977.

A combination of gas chromatography/mass spectrometry was used to investigate the glucuronated metabolites of safrole in the urine of male Sprague-Dawley rats treated with safrole (300 mg/kg/day ip in oil on 4 consecutive days). Six metabolites were found; they were identified as p-cresol glucuronide, propylcatechol glucuronide, allylcatechol glucuronide, eugenol glucuronide, hydroxyepoxysafrole glucuronide, and two monohydroxysafrole glucuronides. (12 refs)

78-1336 Concentration Dependent Inhibition of Myoblast Differentiation by the Co-Carcinogen Phorbol Myristate Acetate (Meeting Abstract). (Eng) Woodbridge, P. (Univ. Minnesota, Minneapolis, MN); Furcht, L. T. *Fed Proc* 37(3): 450; 1978. (no refs)

78-1337 Effects of Phorbol Esters on 2-Deoxy-D-glucose Uptake by C3H/10T1/2 Mouse Embryo Fibroblasts (Meeting Abstract). (Eng) Lillehaug, J. R. (Univ. Southern California Cancer Center, Los Angeles, CA, 90033); Mondal, S.; Heidelberger, C. *Proc Am Assoc Cancer Res* 19: 194; 1978. (no refs)

78-1338 Clonal Heterogeneity of Murine Erythroleukemia Cells (MELC) to Tumor Promoter



**Mediated Inhibition of Cell Differentiation (Meeting Abstract).** (Eng) Fibach, E. (Cancer Center Columbia Univ., New York, NY, 10032); Yamasaki, H.; Weinstein, I. B.; Bank, A.; Rifkind, R. A.; Marks, P. A. *Proc Am Assoc Cancer Res* 19: 238; 1978. (no refs)

**78-1339 Tumor-promoting Activity of 2,3-Dihydrophorbol Myristate Acetate and Phorbol Myristate Acetate in Mouse Skin.** (Eng) Segal, A. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016); Van Duuren, B. L.; Mate, U.; Solomon, J. J.; Seidman, I.; Smith, A.; Melchionne, S. *Cancer Res* 38(4): 921-925; 1978.

The tumor-promoting activity of 2,3-dihydrophorbol myristate acetate (DPMA), phorbolol myristate acetate (PHMA), and phorbol myristate acetate (PMA) was investigated in female ICR/Ha Swiss mice. A single application of DPMA (10 µg/mouse) to the skin produced no observable inflammatory effects after 28 hr. Promotional ability was then tested by thrice weekly applications of the test compounds 2 wk after a single application of 20 µg 7,12-dimethylbenz(a)anthracene. PHMA was tested at 2.5 and 10 µg and PMA was tested at 2.5 µg. The first papillomas were noted at 51-54 days in all three groups: the respective incidences were 24/30, 29/30, and 30/30 mice, and the total number of papillomas was 181, 69, and 317. DPMA and PMA were then compared at a dose of 10 µg. Papillomas were noted at 220 days in the DPMA group and 49 days in the PMA group. The respective incidences were 9/30 and 30/30, and the total number of tumors was 17 for DPMA and 590 for PMA. Chemical procedures for the preparation of DPMA are presented. (18 refs)

**78-1340 Retinoic Acid (RA) Inhibition of 12-Tetradecanoylphorbol-13-acetate (TPA)-Induced Papillomas in Mouse Epidermis (Meeting Abstract).** (Eng) Holder, J. W. (McArdle Lab., Univ. Wisconsin, Madison, WI, 53706); Boutwell, R. K. *Fed Proc* 37(3): 232; 1978. (no refs)

**78-1341 Retinoic Acid Inhibition of the Comitogenic Action of Mezerein and Phorbol Esters in Bovine Lymphocytes.** (Eng) Kensler, T. W. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Mueller, G. C. *Cancer Res* 38(3): 771-775; 1978.

The effects of retinoic acid (RA) on the comitogenic action of mezerein and 12-O-tetradecanoylphorbol-13-acetate (TPA), two potent tumor promoters, were investigated in bovine lymphocytes. Lymphocytes were cultured in the pres-

ence of phytohemagglutinin (PHA), and TPA ( $10^{-9}$ - $10^{-7}$  M) was added at intervals of 0-46 hr. Max comitogenic action was achieved when the two substances were added concurrently. A comparison of the tumor-promoting activity of these agents and their capacity to stimulate DNA synthesis in PHA-pretreated lymphocytes indicated that a good correlation existed between the two activities. Addition of  $10^{-9}$ - $10^{-7}$  M mezerein to PHA-pretreated lymphocytes increased thymidine incorporation over that observed in lymphocytes treated with PHA alone. However, concurrent addition of  $10^{-9}$ - $10^{-7}$  M RA selectively blocked this action. At  $>10^{-7}$  M, mezerein partially overrode the antagonistic effect of RA. The comitogenic action of PHA and  $10^{-8}$  M TPA was also blocked by RA, but if the acid was added  $>3$  hr after TPA and PHA inhibition was greatly diminished. RA had no effect on TPA-mediated induction of RNA and protein synthesis. The inhibition of TPA-induced DNA synthesis was linear at concentrations of 0.01-10 µM. A number of natural and synthetic retinoids were also evaluated, and none were as inhibitory as RA. (24 refs)

**78-1342 Metabolism of Hyperplastic Hamster Cheek Pouch Epithelium (Meeting Abstract).** (Jpn) Harris, R. R. (Dows Inst. Dental Res., Coll. Dentistry, Univ. Iowa, Iowa City, IA); Mackenzie, I. C. *J Dent Res* 57(2): 245; 1978. (1 ref)

**78-1343 Peripheral Nerve Lesions and Carcinogenesis after Long-Term Administration of Cadmium to the Rat.** (Jpn) Sato, K. (Second Dept. Pathology, Kumamoto Univ. Medical Sch., Kumamoto, Japan). *Kumamoto Med J* 51(4): 242-264; 1977.

The neurotoxic and carcinogenic effects of cadmium were examined in Wistar rats inoculated sc with 0.169-0.337 µg CdCl<sub>2</sub> once a month and observed for 1-8 mo. A second group of rats was administered 10-40 ppm CdCl<sub>2</sub> in the drinking water, and they were observed for 18-28 mo. All treated rats developed a motor weakness associated with a hyperion-and-crossing phenomenon of the hindlimb when held upside down by the tail. Histological changes indicative of peripheral neuropathy were found in the spinal roots and sciatic nerves. The predominant pathology was a segmental degeneration of myelin, with marked destruction of the myelin sheaths and phagocytosis of myelin in the Schwann cell bodies. Signs of remyelination (thin myelin sheaths, increased Schwann cells containing ribosomes) were also detected. The axoplasm showed an accumulation of glycogen particles and the formation of glycogenosomes. Of the rats receiving cadmium, 4/10 rats surviving  $>18$  mo developed tumors (fibrosarcomas, 2 fibromas) of the skin. No tumors were found in controls. (35 refs)



344 **Morphologic Transformation of Syrian Hamster Fetal Cells Induced by Nickel Compounds** (Eng) Costa, M. (Inst. Materials Science, Connecticut, Storrs, CT, 06268); Nye, J.; Sunderman, F. W. *Fed Proc* 37(3): 231; 1978. (no refs)

345 **Manganese Inhibition of Nickel Subsulfide Induction of Erythrocytosis in Rats.** (Eng) Hopf, M. (Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032); Sunderman, F. W. *Res Commun Chem Pathol Pharmacol* 19(2): 337-345; 1978.

Effect of manganese on nickel subsulfide-induced erythrocytosis was investigated in male Fischer 344 rats. Intraperitoneal administration of an admixture of Mn dust and  $\text{Ni}_3\text{S}_2$  ( $4.0 \text{ mg Mn} + 1.2 \text{ mg Ni}_3\text{S}_2$  or  $6.9 \text{ mg Mn} + 10 \text{ mg Ni}_3\text{S}_2$ ) induced erythrocytosis. This finding could be used to determine how nickel subsulfide stimulates the production and/or release of erythropoietin in rat kidney. (12 refs)

346 **Effects of Zinc and Retinyl Acetate on Hamsters During Cheek Pouch Carcinogenesis** (Eng) Merchant, H. W. (Sch. Dentistry, Medical Coll. Georgia, Augusta, GA, 30902); B. B.; Kolas, S.; Sobel, R. E. *J Dent Res* 57(A): 177; 1978. (1 ref)

347 **Direct Interaction with Cellular Targets as the Mechanism for Chromium Carcinogenesis.** (Eng) Raffetto, G. (Centro Regionale Oncologico, Università di Genova, Genoa, Italy); Parodi, S.; Parodi, C.; De Ferrari, A.; Croiano, R.; Brambilla, G. *Tumori* 63(6): 503-512; 1977.

Chromium carcinogenesis was investigated in primary fetal B/c mouse cultures. Two valences of Cr were studied:  $\text{Cr}^{3+}$  as  $\text{CrCl}_3$  and  $\text{Cr}^{6+}$  as  $\text{K}_2\text{Cr}_2\text{O}_7$ . The ID50 (50% inhibition of cell growth) of  $\text{Cr}^{3+}$  at 96 hr ( $0.39 \mu\text{g/ml}$ ) was approximately 16 times that of  $\text{Cr}^{6+}$  ( $0.089 \mu\text{g/ml}$ ); that after 1 hr ( $16.83 \mu\text{g/ml}$ ) was about 29 times that of  $\text{Cr}^{6+}$  ( $0.57 \mu\text{g/ml}$ ). Study of transforming activity using the ID25 and ID50 of  $\text{Cr}^{3+}$  and  $\text{Cr}^{6+}$  failed to show a dose dependence of this activity. At equitoxic doses, both valences induced the same degree of morphologic changes and alterations of growth behavior.  $\text{Cr}^{6+}$  produced more chromosomal aberrations. Autographic studies of DNA synthesis in A18BcR cells exposed to equitoxic Cr concentrations (approx equal to the  $\text{Cr}^{6+}$  max) revealed unscheduled DNA synthesis in cells previously exposed to  $\text{Cr}^{6+}$  but not in cells previously exposed to  $\text{Cr}^{3+}$ . These findings suggest that Cr carcinogenesis is due to direct interaction with cellular targets. (15 refs)

78-1348 **Oncological Study in Rats of Ferastral, an Iron-Poly(Sorbitol-Gluconic Acid) Complex, after Intramuscular Administration.** (Eng) Magnusson, G. (Toxicology Labs., Astra Pharmaceuticals AB, S-151 85 Södertälje, Sweden); Flodh, H.; Malmfors, T. *Scand J Haematol* (Suppl. 32): 87-98; 1977.

A study was conducted to determine if Ferastral, a high molecular iron-poly(sorbitol-gluconic acid) complex (IPSG) can induce sarcomas at the injection site after repeated administration to rats in high doses. Imferon, an iron-dextran complex known to cause sarcomas under the same conditions, was included for comparison. Four groups of Sprague-Dawley rats were given IPSG or iron-dextran im 2x/wk for 17 wk; the experiment lasted for 95 wk. Each compound was given in a low and high dose. Depending on the body mass, the dose levels ranged from 2.5 to 10 mg (25-50 mg/kg) and from 5 to 20 mg (50-100 mg/kg) of iron per rat, respectively. The total dose of iron per rat averaged 235 and 495 mg, respectively. Tumors appearing to be sarcomas developed at the im injection sites in almost all the treated animals starting at the 30th experimental week. The sarcomas appeared earlier in the high dose groups than in the low dose groups and slightly earlier in the rats given IPSG than in those given iron-dextran. No other pathological changes, including neoplasms, were considered to be related to the treatment. It is unlikely that the results of this study are applicable to man, since there is no proved human case of sarcomas at the injection site after administration of iron preparations, although the sarcomagenic effects of iron-dextran in animals have been known for 20 yr. (23 refs)

78-1349 **Chromosomal Aberrations in Workers Professionally Exposed to Lead.** (Eng) Deknadt, Gh. (Mammalian Genetics Lab., Dept. Radiobiology, S.C.K.-C.E.N., Mol, Belgium); Manuel, Y.; Gerber, G. B. *J Toxicol Envir Health* 3(5/6): 885-891; 1977.

Chromosome aberrations were analyzed in 16 Frenchmen who worked in a lead battery smelting plant, 7 Belgians who worked in a factory in which tin dishes were made, and 20 controls. The workers were chosen on the basis of elevated blood lead levels (Frenchmen) or elevated urinary  $\delta$ -aminolevulinic acid levels (Belgians). The Belgians had a lower mean age and a shorter exposure time than the Frenchmen. Severe chromosome aberrations, dicentrics, or rings were found only in the Frenchmen; however, there was no correlation between blood lead levels and chromosomal aberrations. The number of aneuploid cells was significantly decreased and the number of cells with structural abnormalities significantly increased in the 9 Belgians, compared with the Frenchmen or controls. More chromatid gaps were noted in the Belgians, but this was significant only in comparison with the Frenchmen. Chromosome gaps were significantly decreased in the Belgians compared with the Frenchmen or controls. It is concluded that there is a small but significant difference



between the two groups that cannot be explained by age or length or severity of exposure. It is suggested that lead is not the only factor responsible for the aberrations found in some lead industry workers and that lead may not cause these aberrations unless it is supported by other factors. (25 refs)

- 78-1350 Mutagenicity of Filtrates from Respirable Coal Fly Ash.** (Eng) Chrisp, C. E. (Radiobiology Lab., Univ. California, Davis, CA, 95616); Fisher, G. L.; Lammert, J. E. *Science* 199(4324): 73-75; 1978.

Incubation of histidine-requiring auxotrophs of *Salmonella typhimurium* (strains TA100, TA1535, TA1537, TA1538, and TA98) with cyclohexane-, saline-, and serum-soluble surface components of respirable fly ash particles collected from a power plant over a 30-day period produced an increased number of revertants in two of the frame-shift tester strains (TA98 and TA1538). Chemical analyses indicated the presence of both organic and inorganic compounds on the fly ash surface. The increased mutagenicity of the serum filtrate compared to the other filtrates indicates that extraction with serum increases the sensitivity of the *Salmonella* technique for detecting the mutagenicity of complex mixtures. It may be expected that substances on the surface of fly ash deposited deep in the lung should be similarly soluble in alveolar fluid. The prospect of a large increase in the amount of coal burned for energy production warrants specific identification of these mutagenic substances and a careful assessment of the possible carcinogenic properties of respirable fly ash. (24 refs)

- 78-1351 Mesothelioma in Shipyard Workers.** (Eng) Hinds, M. W. (Occupational Health Section, State Washington Dept. Social and Health Services, Olympia, WA). *West J Med* 128(2): 169-170; 1978.

The excess of mesothelioma among shipyard workers in the Puget Sound area of Washington state was studied by examining the 1968-1976 death certificates for the four-county area. These workers come into direct and indirect contact with the asbestos used to insulate the steam plant of ships. A total of 52 cases (40 men and 12 women) were found. An analysis of occupations indicated no significant results for residents of two counties, but 30.3% of the men with mesothelioma in the other two counties were employed at the Puget Sound Naval Shipyard. Analysis of the shipyard county alone showed a significant excess of mesothelioma patients to be shipyard employees (88.9% vs 22.2% of controls). The shipyard worker patients had a variety of occupations, indicating the significance of indirect asbestos exposure in the etiology of the disease. (4 refs)

- 78-1352 Follow-up Study of Pleural Hyalinosis in Individuals Not Exposed to Asbestos Dust.** (Eng)

Navratil, M. (Inst. Hygiene and Epidemiology, Center Industrial Hygiene and Occupational Diseases, Praha, Czechoslovakia); Moravkova, K.; Trippe, F. *Environ Res* 15(1): 118; 1978.

A follow-up study was made of 31 pleural hyalinosis patients (60-80 yr) without a history of asbestos exposure. Five-year follow-up studies were possible with 22 patients, during which time no disease with pleural complications had occurred. With the exclusion of three patients who were found to have had short-term asbestos exposure 30-40 yr previously, unchanged x-ray findings were noted in 10, increased calcified layers in 9. Of the three who had been exposed to asbestos, one had no changes and two had a simple progression of calcification. Since no complications or deaths could be attributed directly to the pleural hyalinosis, it is suggested that complications in the form of pleural effusion or mesothelioma are probably connected with the presence of asbestos in the lungs or pleura of persons with long-term exposure (30 refs)

- 78-1353 Asbestos-induced Mesotheliomas in Hamsters: Similarities to Human Mesotheliomas and Presence of Type C Virus Particles (Meeting Abstract).** (Eng) Sobel, H. J. (Veterans Admin. Hosp., East Orange, NJ, 07019); Marquet, E.; Smith, W. E.; Hubert, D. D. *Fed Proc* 37(3): 231; 1978. (no refs)

- 78-1354 Effects of  $\Delta^9$  Tetrahydrocannabinol in Mice (Meeting Abstract).** (Eng) Szepesenwol, J. (Dept. Biological Sciences, Florida International Univ., Miami, FL 33199); Fletcher, J.; Toyo-Goyco, E. *Fed Proc* 37(3): 1978. (no refs)

- 78-1355 Mutagenicity Induced by Lyophilization and Storage of Urine from Isoniazid-treated Patients (Eng)** Miller, C. T. (Toxicology Res. Div., Bureau of Chemical Safety, Health Protection Branch, Health and Welfare Canada, Ottawa, Canada); Stoltz, D. R. *Mutat Res* 56(3): 289-291; 1978.

The mutagenicity of male Sprague-Dawley rat urine treated with *Salmonella typhimurium* TA1535 was investigated following treatment of the rats with a single po dose of isonicotinic hydrazide (isoniazid; INH). INH (0.05-5.0 mg/plate), with or without a rat liver microsomal fraction, was not mutagenic; negative findings were also obtained with INH metabolites. Urine collected during the 24 hr following po treatment with 90-550 mg/kg INH and then lyophilized was mutagenic and the activity was dose-dependent. To test for production of a mutagen during the handling of the urine, INH was added to water, sterile urine, or contaminated urine and



with and without lyophilization. All lyophilized samples containing INH were mutagenic, but the same concentration of INH without lyophilization was not mutagenic. Urine from INH was not mutagenic under any conditions. Urine excreted from the bladder 2.5 hr after a po INH dose of 400 mg/kg did not increase reversion frequency when tested immediately; however, significant mutagenic activity developed during storage at room temperature. Twenty-four-hour urine specimens from INH-treated animals were negative for mutagenicity (without lyophilization) at day 0, but they became mutagenic after 8-14 days at room temperature. (7 refs)

**78-1356 Nicotine in Breast Fluid of Nonlactating Women.** (Eng) Petrakis, N. L. (G. W. Hooper Foundation, Dept. International Health, Univ. California, San Francisco, CA, 94143); Gruenke, L. D.; Beelen, T. C.; Casali, N.; Craig, J. C. *Science* 199(4326): 303-305; 1978.

Nicotine content in the breast fluid of nonlactating smoking and nonsmoking women was analyzed by a combination of gas chromatography, mass spectrometry, and selected ion monitoring. Breast fluid samples were obtained by a standard needle aspiration technique 15 min after a single cigarette had been smoked. Nicotine levels of 46-195 nanograms (ng)/ml were detected in the breast fluid of the smokers; this was considerably greater than the 10- to 20-ng/ml levels previously reported for plasma. Women who smoked one pack per day had levels of 46-60 ng; the one woman who smoked two packs per day had a level of 195 ng. Nicotine was not found in the breast fluid of nonsmokers. Cotinine, the major metabolite of nicotine, was also found at concentrations of 300 ng/ml; the same concentrations were detected in the plasma. These findings indicate that the secretion of exogenous substances into nonlactating breast gland may be a general phenomenon. Tobacco smoke carcinogens such as benzo(a)anthracene and benzo(a)pyrene, which are absorbed through the lungs, probably also reach the breast fluid. (17 refs)

**78-1357 Interaction and pH Dependence of Effects of Nicotine and Carbon Monoxide in Cigarette Smoke Inhalation Experiments with Rats.** (Eng) Stauffer, H. (Dept. Chemistry, Burgdorf Coll. Technology, CH-3400 Burgdorf, Switzerland); Riedwyl, H. *Agents Actions* 7(5/6): 588; 1977.

The toxic properties of combinations of CO and nicotine were investigated in rats. No synergistic effects were observed. From alkaline smoke the absorption of nicotine is sufficiently rapid for it to add to the acute toxicity of CO. Total particulate matter does not contribute significantly to smoke sol toxicity. (15 refs)

**78-1358 Isolation and Identification of New Components in the Ether-soluble Portion of Cigarette Smoke Condensate.** (Eng) Newell, M. P. (Res. Dept., R. J. Reynolds Tobacco Co., Winston-Salem, NC, 27102); Heckman, R. A.; Moates, R. F.; Green, C. R.; Best, F. W.; Schumacher, J. N. *Tobacco Int* 180(3): 70-75; 1978.

The semivolatile compounds of the ether-soluble portion of the smoke condensates from four different 85-mm, nonfiltered, uncased cigarettes were isolated and identified. A total of 643 components were identified in the ether-soluble fractions of the various smoke condensates, 173 of which had not been reported as cigarette smoke constituents. These new isolates included 13 acids, 13 lactones, 2 aldehydes, 56 ketones, 4 alcohols, 15 phenols, 19 nitrogen heterocyclics, 15 aliphatic hydrocarbons, 33 cyclic hydrocarbons, and 3 miscellaneous compounds. A number of these compounds are known to be present in tobacco leaves. (14 refs)

**78-1359 Aza-Arenes in Tobacco Smoke.** (Eng) Dong, M. (Div. Environmental Carcinogenesis, Naylor Dana Inst. for Disease Prevention, American Health Foundation, Vahalla, NY, 10595); Schmeltz, I.; Jacobs, E.; Hoffmann, D. *J Anal Toxicol* 2(1): 21-25; 1978.

Chromatography and mass spectrometry were used to determine the levels of quinoline (a combustion product of tobacco leaf proteins) and other basic azaarenes in tobacco smoke. Quinoline was the most abundant azaarene found; its concentration in a US blend, 85-mm filterless cigarette was 1.67 µg. (36 refs)

**78-1360 The Risk of Bronchogenic Carcinoma in Men who had Smoked over 200 Thousand Cigarettes.** (Cze) Kozak, J. (Oddeleni tuberkulozy a respiracnich nemoci polikliniky, OUNZ, 248 30 Kutna Hora, Czechoslovakia). *Stud Pneumol Phtiseol Cech* 37(10): 681-684; 1977.

One thousand and thirty-three men aged 40-65 yr, who had smoked at least 200,000 cigarettes during their lifetimes, were subjected to x-ray examinations at 6-mo intervals over a 5-yr period. The mean annual incidence of bronchogenic carcinoma was found to be 0.60% in this risk group, vs 0.24% in a control group of 11,451 men (aged > 40 yr) in the general population. (5 refs)

**78-1361 Smoking and Industrial Pollution, and Their Effects on Menopause and Ovarian Cancer.** (Eng) Mattison, D. R. (Dept. Obstetrics and Gynecology, Columbia Presbyterian Medical Center, New York, NY, 10032); Thorgeirsson, S. S. *Lancet* 1(8057): 187-188; 1978.



The ovarian metabolism and ovotoxicity of benzo(a)pyrene (BP) were studied in rats and mice. Mouse and rat ovaries contain nonspecific microsomal monooxygenases that metabolize polycyclic hydrocarbons to reactive species that are toxic, carcinogenic, and mutagenic. A low dose of BP (20 mg/kg) destroyed 25% of the oocytes, but a higher dose (240 mg/kg) destroyed 98% of the oocytes. Once the oocytes are destroyed, menopause is induced. Similar activity may occur in humans, since at age 44-53, women who smoke one or more packs of cigarettes per day are more likely to be post-menopausal than nonsmokers. The frequency of post-menopausal women among those smoking one-half pack per day is intermediate between those smoking one pack and nonsmokers. These findings suggest that the human ovary has the microsomal monooxygenase necessary for metabolizing polycyclic hydrocarbons in cigarette smoke to reactive species capable of destroying oocytes. Events such as mutations or aberrations in development after fertilization could affect oocytes surviving exposures to these reactive metabolites. (17 refs)

- 78-1362 Chimney Sweeper's Disease Revisited: First Case Reported in a Black.** (Eng) Larson, D. L. (Emerson Hall, Room 236, 1100 W. Michigan St., Indianapolis, IN, 46202); Bennett, J. E. *Plast Reconstr Surg* 61(2): 281-283; 1978.

The case report of a 62-yr-old black man with carcinoma of the scrotum is presented. For the previous 20 yr, he had been employed in the plumbing and heating business, and he frequently became exposed to soot from cleaning flues and furnaces. (11 refs)

- 78-1363 Substitute-Tobacco Tar Toxicity (Letter to Editor).** (Eng) Boxall, R. R. (Gallaher Ltd., London WC2B 6TG, England); Field, E. O. *Med J Aust* 1(8067): 773; 1978.

Mutagenicity tests with tobacco substitutes have confirmed previous experiments that the tar from these substitutes is just as mutagenic as the tar from cigarettes without substitutes. However, the yield of tar was lower from the former. Mouse skin-painting tests indicated that the substituted cigarettes produced significantly fewer tumors than all-tobacco cigarettes, but only when a large population of mice was used. Thus, the introduction of substitute material reduces the tar yields of low-tar cigarettes and the potential health benefit, even though it may be slight, should not be dismissed lightly. (4 refs)

- 78-1364 Mutagens in Automobile Exhaust (Meeting Abstract).** (Eng) Wei, E. T. (Univ. California, Berkeley, CA, 94720); Wang, Y. Y.; Talcott, R. E.; Sawyer, R. F.; Rappaport, S. M. *Fed Proc* 37(3): 247; 1978. (no refs)

- 78-1365 Biological Effects of City Smog Extracts. I. Cytotoxicity of City Smog Extracts and of Polycyclic Aromatic Hydrocarbons on Mouse Macrophages In Vitro.** (Ger) Seemayer, N. (Gurlittstrasse 53, D-4000 Dusseldorf, W. Germany); de Ruiter, N.; Manojlovic, N.; Weis, H. *Zentralbl Bakteriol [Orig A]* 165(3/4): 260-268; 1977.

The cytotoxic effect of smog extracts from Dusseldorf, West Germany, on in vitro mouse macrophages (line IC-21) and primary peritoneal mouse macrophages was studied. Four carcinogenic and noncarcinogenic polycyclic aromatic hydrocarbons (PAH), benzo(a)pyrene (BP), 7,12-dimethylbenzanthracene, pyrene, and anthracene, were tested in parallel experiments. City smog extracts in dimethyl sulfoxide soln, with a BP concentration of 1.0 or 3.8 µg/ml, induced a dose-dependent reduction of cell viability and an alteration in cell membrane permeability. In contrast, the PAH produced no detectable cytotoxic effects in the dose ranges analyzed (BP concentration ranged from 0.1 to 10 µg/ml). (16 refs)

- 78-1366 An Approach to Assess the Nature of Proximate Carcinogens for Alternant Aromatic Hydrocarbons (Meeting Abstract).** (Eng) Cavalieri, E. (Eppley Inst. Univ. Nebraska Medical Center, Omaha, NB, 68105); Rogan, E.; Saugier, R. *Proc Am Assoc Cancer Res* 19: 203; 1978. (no refs)

- 78-1367 Inverse Correlation Between Species Life Span and Capacity to Activate Hydrocarbon Carcinogens (Meeting Abstract).** (Eng) Schwartz, A. G. (Temple Univ. Medical Sch., Philadelphia, PA, 19140); Moore, C. I. *Fed Proc* 37(3): 454; 1978. (no refs)

- 78-1368 Birth Defects and Aplastic Anemia: Differences in Polycyclic Hydrocarbon Toxicity Associated with the Ah Locus.** (Eng) Nebert, D. W. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Development, NIH, Bethesda, MD, 20014); Levitt, R. C.; Jensen, N. M.; Lambert, G. H.; Felton, J. S. *Arch Toxicol (Berl)* 39(1/2): 109-132; 1977.

The association between aromatic hydrocarbon responsiveness at the Ah locus and teratogenicity and aplastic anemia was investigated. The incidence of stillborns, spontaneous abortions, and malformations caused by methylcholanthrene or 7,12-dimethylbenz(a)anthracene was much higher in the aromatic hydrocarbon-responsive C57BL/6N, C3H/HeN, and BALB/cAnN inbred mouse strains than in the genetically nonresponsive AKR/N strain. These data suggest that an association exists between the



cus and teratogenesis. Furthermore, the observed differences in teratogenicity had been predicted in advance, on the basis of known differences in polycyclic hydrocarbon metabolism regulated by the *Ah* locus. Aplastic anemia induced by benzo(a)pyrene (BP) occurred in less than 4 wk in the unresponsive *Ahd/Ahd* mouse, whereas responsive *Ahb/Ahb* and *Ahd/Ahd* siblings remained healthy for 6 mo while receiving the same daily dose of BP (120 mg/kg). There was a 2- to 4-wk latent period between exposure of *Ahd/Ahd* mice to BP and death due to bone marrow hypoplasia; morphological changes were apparent early in the latent period. Evidence that the *Ah* locus exists in humans has been obtained from studies using cultured lymphocytes of monozygotic and dizygotic twins. (101 refs)

1369 **Electrochemical Properties of Polycyclic Compounds Studied by the Polarographic Method in Aqueous Systems. IV. Polarographic Study of Carcinogenic and Noncarcinogenic Hydrocarbons in Ethyleneglycol-monomethylether.** (Eng) Vachalkova, A. (Cancer Res. Inst., Czechoslovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Vachalkova, V.; Bahna, L. *Neoplasma* 24(6): 565-571; 1977.

The polarographic reduction potentials of polycyclic hydrocarbons were measured to determine their correlation with carcinogenic activity. The half-wave potentials of polarographic waves I and II of the carcinogenic benzo(a)pyrene analogs were reduced in ethyleneglycol monomethyl ether on mercury dropping electrode at more positive potentials than noncarcinogenic analogs. (12 refs)

1370 **Skin Tumor-initiating Activities of the Twelve Isomeric Phenols of Benzo(a)pyrene.** (Eng) Gutzkow, T. J. (Div. Biology, Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Bracken, W. M.; Dresner, S.; Levin, W.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res* 38(3): 678-681; 1978.

The skin-tumor-initiating activities of the 12 isomeric phenols of benzo(a)pyrene (BP) were evaluated in female CD-1 mice. Hydroxy-BP (11-OHBP) was moderately active, but 2-hydroxy-BP (2-OHBP) and BP were strong tumor initiators when applied topically (400 nanomoles) before twice weekly injections of 12-O-tetradecanoylphorbol-13-acetate (10<sup>-5</sup> g). The remaining 10 BP phenols had <5% of the tumor-initiating activity of BP (when the data were expressed as papillomas/mouse). After 30 wk of tumor promotion, the number of papillomas per mouse was 8.4, 8.5, and 2.8, respectively, in mice treated with BP, 2-OHBP, and 11-OHBP. The latent period was 5 wk for BP and 2-OHBP and 7 wk for 11-OHBP. The time required for 50% of the animals to develop tumors was 13 wk for BP-treated mice and 15 wk for 2-OHBP- or 11-OHBP-treated mice. Additional studies are needed to determine whether 2-OHBP is formed from BP in skin and other tissues. (36 refs)

78-1371 **Nuclear Enlargement and DNA Synthesis in Mouse Epidermis Treated with Carcinogen and Promotor.** (Eng) Ingram, A. J. (British Industrial Biological Res. Assoc., Carshalton, Surrey SM5 4DS, England); Grasso, P. *Exp Pathol (Jena)* 14(5): 233-242; 1977.

Experiments were performed to determine whether a G2 block is involved in the epidermal nuclear enlargement produced by topical application of 0.1 ml of a 1,000- $\mu$ g/ml benzo(a)pyrene (BP) soln and to see how the growth stimulus induced by 0.1 ml of a 0.1% soln of croton oil (CO) affects the response. Female Tuck TO mice were treated twice daily for up to 3 days with BP alone, CO alone, BP followed by CO, or CO followed by BP. CO treatment gave rise to a mitotic stimulus, with a reduction in the ratio of labeled nuclei/mitosis. Repetitive BP treatment gave rise to an increase in the number of labeled nuclei together with a fall in the number of mitoses, producing a high ratio of labeled nuclei/mitosis. The effects of BP were most evident when CO was given as a mitotic stimulus prior to BP treatment. In a second experiment, mice were treated with CO on day 0 and/or BP or nothing on day 1 and killed on day 3 or 6 to determine the fate of enlarged nuclei. A disappearance of enlarged nuclei was seen when mice were kept for 5 days after combined CO and BP treatment, in spite of a reduced cell loss (compared with CO treatment alone). It is concluded that the carcinogen induces a G2 block and that a growth stimulus provided by the promotor induces polyploidy. In the epidermis, enlarged nuclei are lost by desquamation, but occasional large nuclei that persist might be responsible for the emergence of tumors. (19 refs)

78-1372 **Effects of Administration to Mice of Butylated Hydroxyanisole by Oral Intubation on Benzo(a)pyrene-induced Pulmonary Adenoma Formation and Metabolism of Benzo(a)pyrene.** (Eng) Speier, J. L. (Dept. Lab. Medicine and Pathology, 456 Jackson Hall, Medical Sch., Univ. Minnesota, Minneapolis, MN 55455); Lam, L. K.; Wattenberg, L. W. *J Natl Cancer Inst* 60(3): 605-609; 1978.

Administration of butylated hydroxyanisole (BHA: 7 or 15 mg) by po intubation 4 hr before challenge with benzo(a)pyrene (BP: 3 mg, by the same route) inhibited pulmonary adenoma formation in A/HeJ mice. Incubation of BP with liver microsomes from mice that received 15 mg BHA 2, 4, or 8 hr before sacrifice resulted in less binding of BP metabolites to added DNA than that with control microsomes. High-pressure liquid chromatography studies of the metabolites produced by the incubation of BP with liver microsomes from BHA-treated mice showed a decrease in the formation of BP-4,5-oxide and 9-hydroxybenzo(a)pyrene. In contrast, the formation of 3-hydroxybenzo(a)pyrene was increased. The short interval between BHA administration and the observed biochemical changes indicates that BHA exerts a direct effect on the microsomal metabolism of BP. These changes in BP metabolism occurred under conditions of



BHA administration that decreased the neoplastic response to the carcinogen. (9 refs.)

**78-1373 Oxidative Metabolism of Benzo(a)pyrene via Prostaglandin Biosynthesis (Meeting Abstract).**

(Eng) Sivarajah, K. (Lab. Pulmonary Function and Toxicology, Natl. Inst. Environmental Health Science, NIH, Research Triangle Park, NC, 27709); Anderson, M. W.; Eling, T. E. *Fed Proc* 37(3): 607; 1978. (no refs)

**78-1374 The Metabolism of Benzo(a)pyrene in Rabbit Pulmonary Mono-Oxygenase Systems Reconstituted from Purified Components: Activities of Cytochrome P-450 I and II (Meeting Abstract).**

(Eng) Wolf, C. R. (Natl. Inst. Environmental Health Science, NIH, Research Triangle Park, NC, 27709); Ball, L.; Bend, J. R.; Philpot, R. M. *Fed Proc* 37(3): 643; 1978. (no refs)

**78-1375 Metabolism of Benzo[a]pyrene by Cultured Human Colon (Meeting Abstract).**

(Eng) Autrup, H. (Human Tissues Studies Section, Experimental Pathology Branch, Carcinogenesis, NCI, Bethesda, MD, 20014); Jeffrey, A. M.; Trump, B. F.; Harris, C. C. *Fed Proc* 37(3): 451; 1978. (no refs)

**78-1376 Metabolism of [<sup>3</sup>H]Benzo[a]pyrene by Cultured Human Bronchus and Cultured Human Pulmonary Alveolar Macrophages.**

(Eng) Autrup, H. (Building 37, Room 3A09, NCI, Bethesda, MD, 20014); Harris, C. C.; Stoner, G. D.; Selkirk, J. K.; Schafer, P. W.; Trump, B. F. *Lab Invest* 38(3): 217-224; 1978.

The metabolism of (<sup>3</sup>H)benzo(a)pyrene (BP) was studied in cultured human bronchial epithelium and cultured pulmonary alveolar macrophages (PAM) from the same donor (12 with and 1 without lung cancer). After 7 days in culture, the bronchus explant and PAM were exposed to BP and binding to cellular macromolecules was studied. The binding level of BP to DNA and to protein in PAM from the 13 subjects showed 9- and 33-fold interindividual variation, respectively. In PAM, binding of BP to macromolecules and aryl hydrocarbon hydroxylase (AHH) activity were both dependent on the length of culture time and length of exposure to BP. Pretreatment of PAM with benz(a)anthracene increased both the binding level of BP and AHH activity. When coincubated with BP, cycloheximide, 7,8-benzoflavone, or actinomycin D reduced both the level of binding and the activity of AHH. The major PAM metabolites of BP were 7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene (5%-25% of total metabolites), 9,10-dihydroxy-9,10-dihydrobenzo(a)pyrene (16%-39%), and

two peaks containing unidentified polar metabolites. A negative correlation exists in PAM between binding of BP to protein and AHH activity, but no correlation was found between data from the bronchus explant and PAM. This finding suggests that PAM may not be useful as an indicator cell to assess an individual's risk of developing chemically induced cancer. (442 refs)

**78-1377 Formation of Benzo(a)pyrene--DNA Adducts in Peripheral Human Lung Tissue. (Eng) Shinozaki, K.**

(Dept. Biochemistry and Molecular Biology, J. H. Miller Health Center, Univ. Florida, Gainesville, FL, 32610); Cerutti, P. A. *Cancer Lett* 3(5/6): 303-309; 1977.

The formation of covalent adducts between DNA and benzo(a)pyrene (BP) was investigated in the human alveolar macrophage cell line A549 and six cultured explants of normal appearing peripheral human lung. BP (1.3 μM) was added to the culture medium and washed out after 48 hr. Chromatographic analysis of the DNA digests from all cultures indicated that the cells metabolized BP to diastereomeric dihydroxy-9,10-epoxytetrahydro-BP intermediates. These intermediates reacted with the exocyclic amino groups of deoxyguanosine to form N<sup>2</sup>-(10-[7β,8α,9α- and 9β-trihydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene]yl)deoxyguanosine (dGua-BP I and II). Although comparable amounts of dGua-BP I and II were formed in A549 cells, dGua-BP I represented the predominant adduct in the DNA of the lung specimens. It is not known which cell types found in the lung are responsible for BP metabolism and DNA binding. (24 refs)

**78-1378 The Effects of Dietary Thiamin on the Metabolism of Benzo(a)Pyrene (BP) by Rat Hepatic Microsomes (HM) (Meeting Abstract).**

(Eng) Baker, M. (Sch. Pharmacy, Univ. Georgia, Athens, GA, 30602); W. A. E. *Fed Proc* 37(3): 271; 1978. (no refs)

**78-1379 A Model System for Examining the Role of Dietary Fiber in Chemical Carcinogenesis (Meeting Abstract).**

(Eng) Clinton, S. K. (Univ. Illinois, Urbana, IL, 61801); Visek, W. J. *Fed Proc* 37(3): 263; 1978. (no refs)

**78-1380 Binding of Benzo[a]pyrene and Methylcholanthrene to DNA by Horseradish Peroxidase (Meeting Abstract).**

(Eng) Rogan, E. (Univ. Nebraska Medical Center, Omaha, NE, 68101); Katomski, P.; Roth, R.; Cavalieri, E. *Fed Proc* 37(3): 271; 1978. (no refs)



**78-1381  $\beta$ -Glucuronidase Catalyzed Hydrolysis of Benzo(a)pyrene-3-glucuronide and Binding to DNA.** (Eng) Kinoshita, N. (Chemistry Branch, NCI, NIH, Bethesda, MD, 20014); Gelboin, H. V. *Science* 199(4326): 307-309; 1978.

The possibility that benzo(a)pyrene (BP) glucuronides may be converted by  $\beta$ -glucuronidase (GU) to carcinogens was investigated. BP-3-glucuronide was converted by GU to 3-hydroxy-BP (3-OH-BP) and, during this process, an intermediate was formed that was bound covalently to DNA. In the absence of the enzyme, there was a low level of 3-OH-BP binding to DNA; the presence of the enzyme, however, reduced this binding by half. In the absence of GU, there was only negligible binding of BP-3-glucuronide to DNA, but when 116 Fishman units of the enzyme were added, there was a marked stimulation of the binding of a BP derivative to DNA. The binding to DNA was not via free 3-OH-BP and was not related to the release of 3-OH-BP from the glucuronide. These findings suggest that BP glucuronide metabolites may be precursors of DNA-binding carcinogenic intermediates. The carcinogens could be produced in the target cells themselves, or the BP glucuronides could be transported to sites such as the bladder, kidney, or intestines, where GU action could induce binding to DNA. (20 refs)

**78-1382 Binding of Metabolically Activated Benzo(a)pyrene to DNA and Histones of Rat Liver, Lung and Regenerating Liver.** (Eng) Pezzuto, J. M. (Dept. Chemistry, Massachusetts Inst. Technology, Cambridge, MA 02139); Lea, M. A.; Yang, C. S. *Life Sci* 22(1): 105-110; 1978.

The binding of benzo(a)pyrene (BP) metabolites to the DNA and histones of nuclei isolated from the lungs, regenerating liver, or normal liver of Long-Evans rats was investigated. Separation of enzymically degraded DNA by Sephadex LH-20 chromatography yielded several radioactivity peaks, the most prominent of which corresponded to the binding product of the 7,8-diol-9,10 BP epoxide. BP metabolites also bound extensively to the H1 histone fraction. The patterns of BP binding to the lung and regenerating liver nuclei did not differ from that of the binding to normal liver nuclei. Thus, the binding related to BP carcinogenesis in lungs and regenerating liver may involve target molecules other than DNA or histones. Alternatively, other epigenetic factors may be responsible for the differences in tissue susceptibility to BP. (34 refs.)

**78-1383 Nonlinear Dose-Response Relationship for the Binding of the Carcinogen Benzo(a)pyrene to Rat Liver DNA In Vivo.** (Eng) Lutz, W. K. (Inst. Toxicology, Federal Inst. Technology, 8603 Schwerzenbach, Switzerland); Viviani, A.; Schlatter, C. *Cancer Res* 38(3): 575-578; 1978.

The binding of  $^3\text{H}$ -benzo(a)pyrene (BP) to liver DNA of adult male Sprague-Dawley rats was determined 50 hr after a single ip dose of between 40  $\mu\text{g/kg}$ -4 mg/kg. The dose-response relationship was linear up to 1 mg/kg, showed a step toward 2 mg/kg, and gave a shallow linear slope above that value. The binding ranged from 1.7 to 180 nanomoles BP per mole DNA phosphate. To test whether this nonlinearity could be due to an induction of metabolizing enzymes, the microsomal aryl hydrocarbon hydroxylase activity was measured 24 and 48 hr after ip doses of 1, 2, and 4 mg/kg BP to rats of the same strain and age. There was a significant induction of AHH from 4 mg/kg after 24 hr and from 2 and 4 mg/kg after 48 hr; no effects were seen with 1 mg/kg. A purely mathematical extrapolation from the high doses needed in long-term tests to human exposure levels (0.1  $\mu\text{g/kg/day}$ ) would never have predicted a step like the one seen in this study. Such a dose-effect study could, therefore, help to improve the extrapolation of carcinogenicity data to low doses in a biologically founded way. These dose-response curves also give an explanation for the synergistic effects in chemical carcinogenesis; since AHH is inducible by a variety of ubiquitous chemicals in addition to BP, the binding from a given BP dose could be enhanced in an individual exposed to such compounds. (20 refs)

**78-1384 Enzymic Control of Irreversible Binding of Metabolically Activated Benzo(a)pyrene in Perfused Rat Liver by Monooxygenase Activity.** (Eng) Kahl, G. F. (Pharmakologisches Institut, Universität Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Klaus, E.; Jonen, H. G.; Kahl, R. *Arch Toxicol (Berl)* 39(1/2): 149-158; 1977.

Control of benzo(a)pyrene (BP) binding to DNA, RNA, and protein by monooxygenase activity was studied in the isolated perfused rat liver. After the addition of  $^3\text{H}$ -BP to the perfusion medium, 0.1% of the total bound reactivity was irreversibly bound to DNA in the liver from control animals. When the rats were pretreated with the monooxygenase inducers  $\beta$ -naphthoflavone or phenobarbital, BP binding to DNA was increased three to five times. Addition of the monooxygenase inhibitors  $\alpha$ -naphthoflavone or metyrapone to the perfusion medium resulted in a reduction of irreversible binding in liver from both  $\beta$ -naphthoflavone- and phenobarbital-pretreated animals. In livers from control animals, protein and an RNA fraction containing tightly associated protein were able to bind BP metabolites to the same extent, but after induction by pretreatment with  $\beta$ -naphthoflavone, binding to the RNA fraction was much greater than binding to the protein fraction. Phenobarbital pretreatment did not result in an increased irreversible binding to RNA or protein. In control livers, 3% of the added radioactivity was found in the bile after a 1-hr perfusion period, compared with 15%-24% in livers of induced animals. The results indicate that nucleic acid and protein adduct formation in the liver is controlled by monooxygenase activity. (35 refs)



- 78-1385 Species Differences in Activating and Inactivating Enzymes Related to the Control of Mutagenic Metabolites.** (Eng) Oesch, F. (Pharmakologisches Institut, Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Raphael, D.; Schwind, H.; Glatt, H. R. *Arch Toxicol (Berl)* 39(1/2): 97-108; 1977.

The relationship between species and strain differences in monooxygenases and epoxide hydratase and the relative accumulation of benzo(a)pyrene (BP) metabolites mutagenic for *Salmonella typhimurium* strains were investigated. In the presence of a liver homogenate or liver microsomes and NADPH, BP was transformed to metabolites that reverted the *Salmonella* strains tested, but the extent of increase in the number of revertant colonies differed dramatically for the various species and strains. The enzyme activities were modulated by pretreating the rats and mice that were the source of the liver homogenates or microsomes with various inducers or inhibitors of epoxide hydratase or monooxygenase. These manipulations were always accompanied by the corresponding changes in mutagenicity, indicating the causal relationship between enzyme patterns and mutagenic effect. It is concluded that species such as mice, which possess high monooxygenase activity but very low epoxide hydratase activity, are much more susceptible than humans to toxic effects which are mediated by metabolically formed epoxides. (32 refs)

- 78-1386 Dual Role of Epoxide Hydratase in Both Activation and Inactivation of Benzo(a)pyrene.** (Eng) Bentley, P. (Institut Pharmakologisches, Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Oesch, F.; Glatt, H. *Arch Toxicol (Berl)* 39(1/2): 65-75; 1977.

The effect of epoxide hydratase on the mutagenicity of benzo(a)pyrene (BP) was investigated using two *Salmonella typhimurium* strains (TA98 and TA1537) with different susceptibilities to different mutagenic metabolites derived from BP. The assay systems contained microsomes from phenobarbital- or 3-methylcholanthrene (3-MC)-treated mice or from untreated control mice. The pattern of mutagenic metabolites produced from BP by microsomes from 3-MC-treated mice was very different from that produced by microsomes from phenobarbital-treated or control mice, but in each case at least two different metabolites contributed to the mutagenicity. Epoxide hydratase was very efficient at reducing the mutagenic effect when BP was activated by microsomes from untreated or phenobarbital-treated mice, indicating that the principal mutagen produced under these conditions is benzo(a)pyrene 4,5-oxide. When microsomes from 3-MC-treated mice were used, the effect of the hydratase depended on the BP concentration. At low concentrations, mutagenicity was increased by the addition of epoxide hydratase and decreased by inhibition of the hydratase. The reverse was true at high concentrations. These results suggest that the activation of

dihydrodiols contributes significantly to BP mutagenicity when microsomes from 3-MC-treated mice are used and that the role of epoxide hydratase is determined by the monooxygenase form present in the microsomes in the activating system. (19 refs)

- 78-1387 Mixed-Function Oxidase and Epoxide Hydratase (EH) Activities in Nuclear Membranes Prepared from Rat Liver (Meeting Abstract).** (Eng) Mukhtar, H. (Natl. Inst. Environmental Health Science, NIH, Research Triangle Park, NC, 27709); Elmamlouk, T. H.; Bend, J. R. *Fed Proc* 37(3): 270; 1978. (no refs)

- 78-1388 Induction of Rat Hepatic Microsomal and Nuclear Epoxide Hydratase (EH) and Mixed-Function Oxidase (MFO) Activities by Pretreatment with trans-Stilbene Oxide (t-SO) (Meeting Abstract).** (Eng) Elmamlouk, T. H. (Natl. Inst. Environmental Health Science, NIH, Research Triangle Park, NC, 27709); Mukhtar, H.; Fouts, J. R.; Bend, J. R. *Fed Proc* 37(3): 270; 1978. (no refs)

- 78-1389 Ontogeny of Epoxide Metabolizing Enzyme Activities in Steroidogenic Tissues of the Rat (Meeting Abstract).** (Eng) Lee, I. P. (Lab. Environmental Toxicology, NIEHS, Research Triangle Park, NC, 27709); Suzuki, K.; Mukhtar, H.; Bend, J. R. *Environ Health Perspect* 20: 239; 1977. (no refs)

- 78-1390 Modification of DNA by the Benzo(a)pyrene Metabolite Diol-Epoxide r-7,t-8-Dihydroxy-9,10-Oxy-7,8,9,10-Tetrahydrobenzo(a)pyrene.** (Eng) Kakefuda, T. (Chemistry Branch, NCI, NIH, Bethesda, MD 20014); Yamamoto, H. *Proc Natl Acad Sci USA* 75(1): 419; 1978.

The structural modification of the double-stranded, circular DNA of simian virus 40 and plasmid ColE1 by in vitro binding of r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP diol epoxide I) was studied. Stepwise hydrolysis with endonuclease SI and DNase, followed by DNA analysis by thin-layer chromatography, indicated that binding to adenine caused the local denaturation of DNA and a conformational change observed with the electron microscope. Although the binding of BP diol epoxide I to guanine was tenfold greater than that to adenine, it did not create local denaturation of the DNA double helix. When poly(dA-dT) and poly(dG-dC)-poly(dG-dC) were reacted with epoxide I, binding was 24 times more prevalent on



er than the former. However, when the polymers were incubated with endonuclease SI, strand separation was only observed in the former. (21 refs)

1391 **Metabolism and Biological Activity of Benzo[a]pyrene 9,10-Dihydrodiol (Meeting Abstract).** (Eng) Thakker, D. R. (NIH, Natl. Inst. Arthritis, Metabolic and Digestive Diseases, Bethesda, MD, 20014); Yagi, H.; R. E.; Levin, W.; Lu, A. Y.; Chang, R. L.; Wood, A. Buening, M.; Conney, A. H.; Jerina, D. M. *Fed Proc* 33(3): 749; 1978. (no refs)

1392 **Binding of Benzo[a]pyrene 7,8-Diol-9,10-epoxides to DNA, RNA, and Protein of Mouse Liver Occurs with High Stereoselectivity.** (Eng) Koreeda, M. (Dept. Chemistry, Johns Hopkins Univ., Baltimore, MD, 21218); Moore, P. D.; Wislocki, P. G.; Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M. *Science* 199(4330): 778-781; 1978. (18 refs)

The formation, stereostructure, and cellular reactions of the diol-9,10-epoxide metabolites of benzo(a)pyrene (BP) were examined following topical application of BP to the skin of female C57BL/6J mice. Polymer adducts from the diastereomeric diol epoxides, (+)-(7S, 8R, 9R, 10R) and (-)-(7R, 8S, 9R, 10R), were formed stereospecifically from the corresponding 7,8-dihydrodiols. Both diol epoxides reacted with proteins, RNA, and DNA in vivo. With the nucleic acids, preferential binding occurred at the 2-amino group of guanine. Definite conclusions on the relative importance of the diastereomeric BP 7,8-diol-9,10-epoxides in the mutagenicity and carcinogenicity of BP cannot be based solely on quantitative measurements of the amounts of these diol epoxides bound to nucleic acids. The rate of repair and the effect of the diol epoxide-damaged DNA must also be considered. (18 refs)

1393 **Conformation of Dinucleoside Monophosphates Modified with Benzo(a)pyrene 7,8-Dihydrodiol-9,10-Epoxy (Meeting Abstract).** (Eng) Frenkel, K. (Columbia Univ., New York, NY, 10032); Grunberger, D.; Boublik, M.; Weinstein, I. B. *Proc Am Assoc Cancer Res* 19: 192; 1978. (no refs)

1394 **Inactivation of Electrophilic Metabolites by Glutathione S-Transferases and Limitation of the System due to Subcellular Localization.** (Eng) Glatt, H. (Pharmakologisches Institut, Universität Mainz, Obere Zahl-

bacher Strasse 67, D-6500 Mainz, W. Germany); Oesch, F. *Arch Toxicol (Berl)* 39(1/2): 87-96; 1977.

The conjugation of benzo(a)pyrene 4,5-oxide with glutathione and the effect of glutathione on the mutagenicity of benzo(a)pyrene (BP) were investigated in the liver microsome-Salmonella typhimurium mutagenicity assay. The rate of spontaneous conjugation, which occurred very slowly, was slightly augmented by microsomes but very greatly augmented by the cytosol fraction of the liver homogenate, in which the glutathione S-transferases are localized. Glutathione strongly reduced the mutagenicity of BP in the presence of the cytosol fraction, depending on the spatial relationship between microsomes and bacteria in the assay system. The strongest inactivation was found when bacteria and microsomes were in separate agar layers. No activation was observed when all the microsomes were in direct contact with the bacteria. When the premutagen trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene was activated in the presence of the cytosol fraction, glutathione reduced the mutagenicity when microsomes and bacteria were separated from each other but not when all the microsomes were bound to the bacteria. It is concluded that a lipophilic reactive metabolite will preferentially diffuse from the microsomes directly to the target bacteria if this possibility physically exists. For the eukaryotic cell, this implies that enzymes of the cytosol may be of limited value for the inactivation of highly lipophilic reactive metabolites. Reactive metabolites, which are formed in the endoplasmic reticulum, may reach the nucleus by lateral diffusion through the lipid matrix without significant contact with the cytosol. (11 refs)

78-1395 **Metabolism of Benzo(a)pyrene-4,5-oxide (BPO) in the Isolated Perfused Rat Liver (IPL) (Meeting Abstract).** (Eng) Smith, B. R. (Natl. Inst. Environmental Health Science, NIH, Research Triangle Park, NC, 27709); Ball, L. M.; Bend, J. R. *Fed Proc* 37(3): 643; 1978. (no refs)

78-1396 **Activation of Xenobiotics by Monooxygenases: Cultures of Mammalian Cells as Analytical Tool.** (Eng) Wiebel, F. J. (Abteilung Toxikologie, Gesellschaft für Strahlen- und Umweltforschung München, Ingolstädter Landstrasse 1, D-8042 Neuherberg, W. Germany); Brown, S.; Waters, H. L.; Selkirk, J. K. *Arch Toxicol (Berl)* 39(1/2): 133-148; 1977.

The limitations and possibilities of using cultured mammalian cells in the analysis of xenobiotic metabolism by microsomal monooxygenases were examined. Inducible aryl hydrocarbon hydroxylase (AHH) activity occurs in a wide variety of cells in culture (including cells from rodents and man; from adult, newborn, and fetal organisms; and from hepatic and extrahepatic tissues) and in cells transformed by chemicals or viruses. However, the low content of monooxygenases in



established cell lines precludes their purification and functional characterization. In cultured mouse and hamster fetal cells, benzo(a)pyrene (BP) was oxygenated preferentially at the benzo ring to give 9-OH-BP and 3-OH-BP as the major products, whereas liver microsomes preferentially attacked the pyrene side of the molecule. These results suggest that cells in long-term culture are unsuitable as models for hepatic metabolism and drug activation and as a general screening tool for potentially hazardous xenobiotics. In some cultures the low monooxygenase content may be overcome by a cyclic nucleotide phosphodiesterase inhibitor, such as aminophylline, which may increase polycyclic hydrocarbon-induced monooxygenase 2 times and, in some cell lines, more than 10 times. Studies with somatic cell hybrids between RAG cells, an established mouse line, and normal human bone marrow cells have resulted in the preliminary assignment of a locus required for AHH expression to human chromosome 2. Further localization of the structural and regulatory genes on human chromosomes by cell hybridization techniques may make possible the constructing of cells that contain specific sets of human monooxygenases and of other drug-metabolizing enzymes. (54 refs)

**78-1397 Comparison of Aryl Hydrocarbon Hydroxylase (AHH) in Fresh Lymphocytes Versus a B-Lymphocyte Line (RPMI-1788) (Meeting Abstract).** (Eng) Freedman, H. J. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Parker, N. B.; Gurtoo, H. L.; Paigen, B.; Minowada, J. *Fed Proc* 37(3): 597; 1978. (no refs)

**78-1398 Aryl Hydrocarbon Hydroxylase Inducibility in Cultured Lymphocytes from Lung Cancer Patients (Meeting Abstract).** (Eng) Rasco, M. A. (Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner, Houston, TX, 77030); Yamauchi, T.; Johnston, D. A.; Shaw, C. R. *Proc Am Assoc Cancer Res* 19: 189; 1978. (no refs)

**78-1399 Aryl-Hydrocarbon Hydroxylase Inducibility in Patients with Bronchogenic Carcinoma (Meeting Abstract).** (Eng) Lieberman, J. (Respiratory Disease Section, UCLA San Fernando Valley Medical Program, Veterans Admin. Hosp., Sepulveda, CA). *Clin Res* 26(2): 163A; 1978. (no refs)

**78-1400 Differential Induction of Aryl Hydrocarbon Hydroxylase and Cytochrome P-448 Levels in Liver, Testis and Prostate Gland (Meeting Abstract).** (Eng)

Suzuki, K. (NIEHS, NIH, Res. Triangle Park, NC, 27709); Lee, I. P. *Fed Proc* 37(3): 504; 1978. (no refs)

**78-1401 Differences Between Nuclear and Microsomal Cytochrome P-450 in Uninduced and Induced Rat Liver.** (Eng) Rogan, E. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB, 68105); Cavalieri, E. *Mol Pharmacol* 14(1): 215-219; 1978.

The reduced CO and ethyl isocyanide difference spectra of nuclear cytochrome P-450 was investigated in uninduced, phenobarbital (PB)-, and 3-methylcholanthrene (3-MC)-induced male Sprague-Dawley rat liver nuclei. Monooxygenase activities were induced in the rats by ip injection of 25 mg/kg 3-MC 24 hr before killing or twice daily ip injections of 37 mg/kg PB for 3 days. Reduced CO binding difference spectra for microsomal cytochrome P-450 from all three groups of animals showed the expected spectral max. However, the spectra of nuclear cytochrome P-450 were significantly different from those of the corresponding microsomal cytochrome for every set of nuclear membranes and microsomes prepared. Spectra of the nuclear membranes were identical with those of whole nuclei, except that the nuclei exhibited a peak at about 420 nm as a result of Hb contamination. With ethyl isocyanide binding difference spectra, nuclear cytochrome was clearly different from that of microsomal cytochrome. Furthermore, the spectral characteristics for nuclear cytochrome P450 from 3-MC-induced animals were different from those for the nuclear cytochrome P-450 of PB-induced and uninduced animals. The spectra data indicate that the structural form of nuclear cytochrome P-450 differs from that of microsomal cytochrome P-450. (28 refs)

**78-1402 9,10-Dihydrodiols of 1-Hydroxy-3-methylcholanthrene: Potential Proximate Carcinogens Derived from 3-Methylcholanthrene (Meeting Abstract).** (Eng) Thakker, D. R. (NIH, Bethesda, MD, 20014); Levin, W.; Wood, A. W.; Conney, A. H.; Stoming, T. A.; Jerina, D. M. *Proc Am Assoc Cancer Res* 19: 200; 1978. (no refs)

**78-1403 The Localization and Significance of Gamma Glutamyl Transpeptidase Activity in Normal and Neoplastic Mouse Skin (Meeting Abstract).** (Eng) De Young, L. M. (Univ. Wisconsin, Madison, WI, 53706); Bonzelet, W.; Boutwell, R. K. *Fed Proc* 37(3): 597; 1978. (no refs)

**78-1404 Effect of Estradiol and Thyroxine on Tumorigenesis in Mouse Skin (Meeting Abstract).**



(Eng) Lupulescu, A. P. (Medical Res. Building, Wayne State Univ., Detroit, MI, 48201); Rogers, J. H. *Fed Proc* 37(3): 451; 1978. (no refs)

**78-1405 Hepatic Mono-oxygenase Activity and Hepatocellular Morphology in Chickens Treated with 3-Methylcholanthrene.** (Eng) Buynitzky, S. J. (Dept. Pharmacology, Univ. Minnesota Sch. Medicine, Minneapolis, MN, 55455); Wade, A. E.; Munnell, J. F.; Ragland, W. L. *Drug Metab Dispos* 6(1): 1-7; 1978.

Hepatic monooxygenase activity was investigated in male White leghorn chickens given 3-methylcholanthrene (3-MC, 10 mg/kg ip) 72 and 48 hr before killing. Levels of hepatic cytochrome P-450 were increased fourfold in the treated birds, and there was a shift in the Soret peak ( $\lambda_{max}$ ) in the CO-difference spectrum of reduced cytochrome P-450 from 422 (control value) to 448 nanometers. In the 3-MC-treated chickens, in vitro microsomal ethylmorphine N-demethylase (ND) activity was enhanced 1.7-fold, aniline hydroxylase (AH) was increased 2.5-fold, aryl hydrocarbon hydroxylase was increased 20-fold, and NADPH-cytochrome c reductase was unchanged. The  $V_{max}$  was increased for both ND and AH activities; the  $K_m$  for demethylation was depressed, but that for the hydroxylation of aniline was increased. Analysis of hexobarbital sleeping times in control and 3-MC-treated chickens indicated that in vivo hexobarbital metabolism was not enhanced by 3-MC. Electron microscopy revealed proliferation and pronounced vesiculation of the hepatic endoplasmic reticulum. These morphological changes and the accompanying pattern of enhanced monooxygenase activity are features that differ significantly from those of the rat. (35 refs)

**78-1406 Sensitization by Methylcholanthrene in Induction of Skin Tumors.** (Rus) Neiman, I. M. (Lab. Carcinogens, Inst. Nutrition, Moscow, USSR); Andrianova, M. M. *Vopr Onkol* 23(11): 75-79; 1977.

The effect of enteral sensitization with methylcholanthrene (MC) on the development of skin tumors was evaluated in random-bred and C57Bl/CBA mice. The mice received MC (0.25 mg in 1 drop sunflower seed oil, 1x/wk, wk); 8 wk after the last dose, they were given skin applications of MC (1 drop of 0.5% soln, 1x/wk, for 16 wk). Then the sensitized and nonsensitized animals were inoculated ip with  $4 \times 10^6$  lymphocytes from syngeneic 1- to 7-day old mice, and 17 days later, immunized with sheep RBC. On day 4 after immunization, the animals were sacrificed and the number of antibody-forming cells (AFC) in the spleen was assessed. Enteral sensitization increased the number of mice with skin papillomas and carcinomas: 58.3% of the random-bred and 47% of the C57Bl/CBA sensitized mice developed skin carcinomas compared with 25% and 30.1%, respectively, of the nonsensitized mice. It also decreased the av latent period of tumorigenesis

by 1.8 wk. Immunodepression was more pronounced in sensitized mice: the av number of AFC in sensitized mice with carcinomas was 1.4, compared with 6.0 in nonsensitized mice with carcinomas and 556.7 in untreated controls. (18 refs)

**78-1407 Pathogenesis of Spontaneously Metastasizing Mammary Carcinomas in Rats.** (Eng) Kim, U. (Dept. Pathology, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263). *Gann Monogr Cancer Res* (20): 73-81; 1977.

Splenectomy and thymectomy (S and T) were performed in W/Fu rats with 3-methylcholanthrene (3-MC)-induced mammary carcinomas in an attempt to mimic the metastatic picture in man. In the first experiment, rats were fed 200 mg 3-MC in 10 divided doses during a 5-wk period. One or 2 days later, the rats underwent T, S, T + S, or no treatment. In the second experiment, a similar protocol was followed except T and S were performed 1 wk prior to 3-MC feeding. In experiment 1, the overall tumor incidence was increased 20% by T, 31% by T + S over untreated rats. Thirteen of the total 213 tumors regressed completely and spontaneously; most regressions (6) occurred in splenectomized hosts. After excision of the larger tumors, 16 additional tumors regressed in the same hosts. Thus, surgical excision of the early tumors stimulated host immune responses against the later-appearing tumors. In experiment 2, only 144 tumors were induced; however, 31 regressed spontaneously and 22 regressed after excision of the larger tumors. In the first experiment, 5/30 tumors in control animals metastasized to the regional lymph nodes upon their first passage in syngeneic animals; 8/22 tumors in the T group metastasized, chiefly to the lungs; 10/25 tumors in the S group metastasized to the lymph nodes and lungs (2 of these lost their metastatic potential by the second passage); and 6/22 T + S tumors metastasized to the lymph nodes and lungs. Bone metastases were frequently found in S rats. Only three tumors were completely rejected, and all came from the T group. In the second experiment, the incidence of metastases decreased only slightly in spite of the reduced tumor yield: 3/17 in the control group, 2/19 in the T group, 10/28 in the S group, and 7/18 in the T + S group. Ten of 82 tumor grafts were rejected. (37 refs)

**78-1408 Restoration of Growth Control in Malignantly Transformed Mouse Fibroblasts Grown in a Chemically Defined Medium.** (Eng) Tomei, L. D. (Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY 14263); Bertram, J. S. *Cancer Res* 38(2): 444-451; 1978.

The expression of growth control and morphological transformation was studied in methylcholanthrene (MC)-transformed C3H/10T(1/2) CL8 mouse embryo fibroblast



cells serially propagated in chemically defined nutrient medium (CDM). This cell line was successfully adapted to long-term cultivation in CDM by first exposing the cells to albumin (0.1%) before dispersing them with trypsin (50  $\mu\text{g}/\text{ml}$ ). In serum-supplemented media, MCA-transformed C3H/10T(1/2) CL8 cells exhibited such properties of the transformed phenotype as irregular morphology, extensive cell overlap, lack of density-dependent inhibition of division, a saturation density of  $1.1 \times 10^5$  cells/sq cm, and tumorigenicity in vivo. Growth in CDM, however, was associated with a reversible loss of the transformed phenotype: the transformed cells adapted to CDM exhibited a regular epithelioid morphology with no cell overlap and formed confluent monolayers of nonproliferating cells at a saturation density of  $5 \times 10^4$  cells/sq cm. Reversion to the transformed phenotype followed addition of albumin (0.1%) or serum (2%) to logarithmic-phase cultures or exposure to trypsin (10  $\mu\text{g}/\text{ml}$  for 30-60 sec). Cultures in CDM reexposed to serum remained highly tumorigenic in vivo. The results suggest that absorbed serum proteins may block transformation-sensitive cell surface sites responsible for growth control and that these sites are inactivated by trypsin. (28 refs.)

- 78-1409 The Mitigating Effect of Dietary Antioxidants on Chemically-induced Carcinogenesis.** (Eng) Chan, J. T. (Dept. Dermatology, Baylor Coll. Medicine, Houston, TX, 77030); Black, H. S. *Experientia* 34(1): 110-111; 1978.

The effect of a dietary antioxidant mixture (2% wt/wt) on 3-methylcholanthrene (3-MC)-mediated carcinogenesis was investigated in hairless mice. The dorsal median of each animal was painted once with 100  $\mu\text{l}$  3-MC, and 100  $\mu\text{l}$  croton oil was applied once weekly for 15 wk. The antioxidant mixture (1.2% ascorbic acid, 0.5% butylated hydroxytoluene, 0.2% DL- $\alpha$ -tocopherol, and 0.1% glutathione) significantly reduced the frequency of premalignant lesions as early as 12 wk. Tumors appeared in both groups at the same frequency after 14 wk of treatment. However, 33 wk after treatment, tumor frequency in the control group was twice that of the antioxidant-supplemented group. These results suggest that antioxidants not only act upon the initiation of tumorigenesis but also affect the development of tumors from premalignant lesions upon chemical promotion. The results also suggest that there may be a confluence in the developmental steps of both chemical and UV-induced carcinogenesis. (18 refs)

- 78-1410 Metabolic Activations of Polycyclic Hydrocarbons. Structure-Activity Relationships.** (Eng) Lehr, R. E. (Dept. Chemistry, Univ. Oklahoma, Norman, OK, 73019); Jerina, D. M. *Arch Toxicol (Berl)* 39(1/2): 1-6; 1977.

Quantum mechanical calculations were performed to assess the possible role of diol epoxides in polycyclic aromatic hydrocarbon (PAH) mutagenesis and carcinogenesis. The calculations permit a prediction of relative reactivity (ease of carbonium ion formation) for diol epoxides derived from a single PAH and also for diol epoxides from different PAHs. The predictions of the calculations were tested by examining the metabolic activation of derivatives of benzo(a)anthracene (BA) to mutagenic species. The metabolites of BA 3,4-dihydrodiol caused more than 10 times as many mutations in *Salmonella typhimurium* strain TA100 as did metabolites from the other dihydrodiols. The diol epoxides derived from BA 8,9- and 10,11-dihydrodiols had only 3%-7% of the mutagenicity of the diol epoxides derived from BA 3,4-dihydrodiol. Correlations of both the chemical reactivity and the mutagenicity of the diol epoxides with the results predicted by these calculations have thus far been highly successful, although only a limited number of diol epoxides have been tested. Some exceptions have been observed, eg, the relative carcinogenicity of dibenzo(a,h)anthracene and BA predicted by these calculations does not agree with experimental observations. Whether this is a consequence of metabolic differences or calculation deficiencies is not known. (22 refs)

- 78-1411 Evidence for an Unstable 3,4-Epoxy as a Metabolic Intermediate of Benz(a)anthracene.** (Meeting Abstract). (Eng) Yang, S. K. (Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014); Fu, P.; Roller, P. P.; Harvey, R. G.; Gelboin, H. V. *Fed Proc* 37: 597; 1978. (no refs)

- 78-1412 Exceptional Carcinogenic Activity of Benzo(a)anthracene 3,4-Dihydrodiol in the Newborn Mouse and the Bay Region Theory.** (Eng) Wislocki, G. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey, Omaha, NB 68105); Kapitlnik, Levin, W.; Lehr, R.; Schaefer-Ridder, M.; Karle, J. M.; Jerina, D. M.; Conney, A. H. *Cancer Res* 38(3): 693-696; 1978.

Benzo(a)anthracene (BA) and five of its isomeric dihydrodiols were tested for carcinogenicity in newborn Swiss-Webster mice. On days 1, 8, and 15 of life, the mice were inoculated with 400, 800, and 1,600 nanomoles, respectively, of the hydrocarbons. Of mice treated with trans-3,4-dihydroxy-3,4-dihydro-BA (BA 3,4-dihydrodiol), 24% had malignant lymphomas when killed at age 22 wk. In contrast, only 4% of the animals treated with BA developed malignant lymphomas. The 1,2-, 5,6-, 8,9-, and 10,11-dihydrodiols did not induce lymphomas, and they caused few or no pulmonary adenomas. In mice treated with BA and BA 3,4-dihydrodiol, the average number of adenomas per animal was 1.59 and 5.0, respectively. The potent carcinogenicity of BA 3,4-dihydrodiol is consistent with the metabolism of this compound.



ound to one or both of the diastereomeric bay region BA 4-diol-1,2-epoxides. The data, therefore, support the concept that these diol-epoxides are the ultimate carcinogenic metabolites of BA. (42 refs.)

**78-1413 Effect of Compounds which Increase Activity of the Anticoagulative System in Tumor-Bearing Animals on Metastatic Growth and Ultrastructure of Metastatic Cells.** (Rus) Kudryashov, B. A. (Dept. Animal Physiology, State Univ., Moscow, USSR); Kolomina, S. M.; Chentsov, Yu. S.; Kalishevskaya, T. M.; Pogodina, L. S. *Vopr Onkol* 23(12): 77-81; 1977.

The effect of heparin (200 units/100 g) + fibrinolysin (800 units/100 g) + 2.5% chlorpromazine (0.6 ml/100 g) on metastatic spread was studied in Wistar rats with sc transplanted Walker carcinomas and CC57 mice with 9,10-dimethyl-1,2-benzanthracene-induced tumors. This simulation of anticoagulation system hyperfunction significantly inhibited metastatic spread: the degrees of hematogenic and lymphogenic metastatic dissemination were 33.0%, and 5.0%, respectively, compared with 75.0% and 63.0% in controls. Cytologic analysis of the metastatic nodes of the treated animals revealed marked degenerative changes (pyknotosis, a reduced number of mitochondria and polysomes, absence of fibrin fibers). (no refs)

**78-1414 Quantitative Carcinogenesis in Rat Skin with 7,12-Dimethylbenz(a)anthracene (DMBA) and Ionizing Radiation (Meeting Abstract).** (Eng) Burns, F. J. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Strickland, T.; Albert, R. E. *Proc Am Assoc Cancer Res* 19: 237; 1978. (no refs)

**78-1415 Activation of C-Type Virus During Chemically Induced Leukemogenesis in Mice.** (Eng) Nexo, J. (Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205); Ulrich, K. *Cancer Res* 38(3): 729-735; 1978.

The activation of C-type viruses in BALB/c, C3H, DBA/2, and ST/a mice during 7,12-dimethylbenz(a)anthracene (DMBA)-induced leukemogenesis was investigated. All mice except BALB/c were given topical applications of 0.5% DMBA twice weekly for 73-96 days. BALB/c mice were treated topically twice weekly with 50 µl of 0.25% DMBA for 143-157 days. Leukemia incidence was 100% in DBA/2 and ST/a mice, 10% in C3H mice, and 50% in BALB/c mice. Studies with ST/a and DBA/2 mice revealed increased concentrations of the viral protein p30 in the blood and lymphoid

tissues. Most of the p30 in the blood copurified with the RBC, and high protein levels were preferentially found in mice with low spleen wts. DMBA treatment had little effect on p30 expression in C3H and BALB/c mice. DBA/2 mice were sacrificed a few days after 16 DMBA treatments, and their splenocytes were cocultivated with SC-1 mouse and SIRC rabbit cells. DMBA treatment increased the number of animals that were positive in cocultivation with SC-1 cells, and the number of infective centers on the SC-1 cells reflected the concentration of p30 in the blood. This treatment decreased the number of mice that were virus-positive in cocultivation with SIRC cells. However, a few spleens from DMBA-treated rabbit cells did yield SIRC-tropic viruses that gave the highest number of infectious centers. These findings indicate an association of C-type virus activation with chemical leukemogenesis, but they do not necessarily imply an etiological role. (35 refs)

**78-1416 Tumor Promotion and the Induction of Epidermal Ornithine Decarboxylase Activity in Mechanically Stimulated Mouse Skin.** (Eng) Clark-Lewis, I. (Sch. Biological Sciences, Flinders Univ. S. Australia, Bedford Park, S. Australia 5042, Australia); Murray, A. W. *Cancer Res* 38(3): 494-497; 1978.

Wounding by incision promoted tumor development in Swiss albino mouse skin previously initiated with 7,12-dimethylbenz(a)anthracene (25 µg in 0.2 ml acetone). Skin massage elicited a marked proliferative response in epidermal cells, but it was not a promoting stimulus. Wounding of mouse skin, by multiple scalpel incisions or by stripping with silicon carbide paper, markedly increased ornithine decarboxylase (OD) activity. In both instances, activity was max between 20 and 26 hr after wounding, with a secondary rise at 72 hr. Skin massage did not increase activity over the same time period. These results support the suggestion that induction of OD activity is associated with skin tumor promotion. (23 refs.)

**78-1417 Metabolism of 7,12-Dimethylbenz(a)anthracene by Macrophages and Uptake of Macrophage-derived Metabolites by Respiratory Tissues In Vitro.** (Eng) Palmer, W. G. (Chemical Carcinogenesis Program, Frederick Cancer Res. Program, NCI, Frederick, MD, 21501); Allen, T. J.; Tomaszewski, J. E. *Cancer Res* 38(4): 1079-1084; 1978.

The metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) by macrophages from male C3H/He mice and the uptake of the macrophage-derived metabolites by respiratory tissue were studied in vitro. Cultured macrophages and tracheal and lung tissue each produced the same ethyl acetate-soluble derivatives of DMBA. The derivatives produced in different cultures were indistinguishable by chromatography



but differed in their relative proportions. The greatest difference was observed between lungs and macrophages. The predominant metabolite of the former was 8,9-dihydro-8,9-dihydroxy-DMBA, but the latter produced equal quantities of both 8,9-dihydro-8,9-dihydroxy-DMBA and a second uncharacterized derivative, metabolite B, at low DMBA doses ( $<0.05 \mu\text{g/ml}$  medium) and primarily metabolite B at doses  $>0.05 \mu\text{g/ml}$ . The macrophages released the majority of the ethyl acetate-soluble metabolites into the surrounding medium. With the exception of 8,9-dihydro-8,9-dihydroxy-DMBA, these derivatives were accumulated within tracheal and lung tissue when these organs were cocultivated with macrophages in the presence of DMBA. It is suggested that the release of polycyclic aromatic hydrocarbon (PAH) metabolites from macrophages may be an important factor in the increased incidence of lung and bronchogenic tumors resulting from the binding of PAH to particulate dusts. (20 refs)

- 78-1418 In Vitro Development of Oncogenicity in Cell Lines Established from Tracheal Epithelium Preexposed In Vivo to 7,12-Dimethylbenz(a)anthracene (DMBA) (Meeting Abstract).** (Eng) Marchok, A. C. (Cancer and Toxicology Program, ORNL, Oak Ridge, TN, 37830); Nettesheim, P. *Fed Proc* 37(3): 451; 1978. (no refs)

- 78-1419 Morphological Aspects of Early Stages of Carcinogenesis in the Central Nervous System.** (Rus) Avtsyn, A. P. (No affiliation given); Yablonovskaya, L. Ya. *Vestn Akad Med Nauk SSSR* (10): 39-43; 1977.

Characteristic morphological features of the early stages of dimethylbenz(a)anthracene (DMBA) carcinogenesis are described. Within 24 hr after a DMBA pellet was implanted into a rabbit brain, it was starting to become encapsulated by mononuclear cells. Eight days later, these cells began to develop apical processes. These processes reached a max on days 50-60 after carcinogen implantation, a period defined as the villous-cell-maturation stage. Electron microscopy of the villous cells surrounding the DMBA pellet showed that they had multiple lipidlike inclusions, structures that probably take part in DMBA resorption and utilization. (21 refs.)

- 78-1420 Separation of Factors that Inhibit or Stimulate DMBA-induced Breast Tumors from both Fetal and Adult Rat Tissue (Meeting Abstract).** (Eng) Noval, J. J. (Surgery Dept., Temple Univ. Medical Sch., Philadelphia, PA, 19140); Obando, M.; Reichle, R. M.; Ryzlak, M. T.; Reichle, F. A. *Fed Proc* 37(3): 231; 1978. (no refs)

- 78-1421 Studies on the Behaviour of Induced Premalignant Lesions in the Hamster Cheek Pouch (Meeting Abstract).** (Eng) Ferguson, J. W. (Dept. Oral Biology, Univ. Otago, Dunedin, New Zealand). *J Dent Res* 57(A): 75; 1978. (1 ref)

- 78-1422 The Inhibition of Cerebrum Biochemistry in Pups Exposed to Dimethylbenzanthracene (DMBA) During Gestation (Meeting Abstract).** (Eng) Pitkow, H. S. (Pennsylvania Coll. Podiatric Medicine, Philadelphia, PA, 19107); Citron, A.; Ehrlich, T.; Ambrits, M. A.; Davis, R. H. *Fed Proc* 37(3): 853; 1978. (no refs)

- 78-1423 Ultrastructural Studies of DMBA-induced Tumorigenesis in Hamster Cheek Pouch (Meeting Abstract).** (Eng) Papanicolaou, S. J. (Ohio State Univ. Columbus, OH); Cavalari, C. J. *J Dent Res* 57(A): 218; 1978. (no refs)

- 78-1424 Changes in Acetylation Activity in 7,12-Dimethylbenz(a)anthracene-induced Tumors.** (Rus) Bulovskaya, L. N. (Lab. Endocrinology, N. N. Petrov Scientific Res. Inst. Oncology, Leningrad, USSR). *Vopr Onkol* 24(1): 60-64; 1978.

The role of acetylation reactions in neoplastic transformation was studied in three experiments with C57BL and albino random-bred mice. In experiments 1 and 2, C57BL and random bred mice, respectively, received a single sc injection of 7,12-dimethylbenz(a)anthracene (DMBA: 2 mg/mouse). In experiment 3, C57BL mice received an application of DMBA (20  $\mu\text{g/mouse}$ ) to the skin once or twice a week for 15 wk. Hepatic N-acetyltransferase (AT) activity was assessed before and after carcinogen administration. The average latent period was 27, 21, and 28 wk in Groups 1, 2, and 3, respectively. All Group 1 (9/9) and Group 2 (8/8) rats developed sarcomas, but only 1/9 Group 3 rats developed a sarcoma. 4 of these rats developed skin carcinomas, and 4 developed benign tumors. The first increase in AT activity was detected 12 wk prior to the development of sarcomas in Groups 1 and 2; the second peak was recorded after sarcoma development. Similar results were obtained in Group 3, in which the initial increase in AT activity could be detected 16 wk prior to tumor development (benign as well as malignant). These findings indicate that changes in AT activity precede the clinical manifestation of DMBA-induced tumors. Thus, they might be used as an early sign of neoplasia. (14 refs)

- 78-1425 An Ultrastructural, Morphometric and Autoradiographic Study of the Effects of 7,12-**



**78-1425** Methylbenzanthracene on the Rat Adrenal Cortex. (Eng) Alloni, A. S. (Dept. Anatomy, Lab. Electron Microscopy, Univ. Padua, I-35100 Padua, Italy); Mazzocchi, G.; Robba, G.; Gambino, A. M.; Nussdorfer, G. G. *Virchows Arch [Cell Pathol]* 26(3): 195-214; 1978.

Male albino Wistar rats were treated for up to 9 days with injections of 25 mg/kg 7,12-dimethylbenz(a)anthracene, and the effects on the adrenal cortex were observed. A decrease in cell volume and number was noted in the zona glomerulosa; the zona fasciculata showed only a decrease in cell volume; no changes were noted in the zona glomerulosa. The outer two layers demonstrated an increase in mitoses and S phase cells, indicative of a repair mechanism. (53 refs)

**78-1426** Comparative Carcinogenicity of 7-Methylbenz(a)anthracene and Some of its Derivatives at the Methyl Group (Meeting Abstract). (Eng) Roth, R. (Eppley Inst., Univ. Nebraska Medical Center, Omaha, NB, 68105); Grandjean, C.; Cavalieri, E. *Proc Am Soc Cancer Res* 19: 203; 1978. (no refs)

**78-1427** Binding of 7-Hydroxymethyl-12-methylbenz(a)anthracene to Calf Thymus DNA: The Presence and Absence of 3'-Phospho-adenosine-5'-phosphosulfate (PAPS) Generating System (Meeting Abstract). (Eng) Flesher, J. W. (Dept. Pharmacology, Univ. Kentucky Coll. Medicine, Lexington, KY, 40506); Tay, L. *Fed Proc* 37(3): 749; 1978. (no refs)

**78-1428** The Effect of Dietary Protein Level on the In Vivo Covalent Binding of Dibenz(a,h)anthracene (DBA) to Hepatic and Lung DNA as a Function of Pretreatment with MFO Modifiers (Meeting Abstract). (Eng) Falahee, K. J. (Cornell Univ., Ithaca, NY, 14853); Campbell, T. C. *Fed Proc* 37(3): 262; 1978. (no refs)

**78-1429** Metabolism of Anthracene by Liver Mitochondria from Control and Induced Rats (Meeting Abstract). (Eng) Seifried, H. E. (NIH, Bethesda, MD, 20014); Jerina, D. M.; Steinberg, M. *Fed Proc* 37(3): 749; 1978. (no refs)

**78-1430** Effect of Duration of Exposure to Carbon Tetrachloride on Liver Damage in Rats. (Rus) Mashevskaya, T. I. (A. N. Sysin Inst. General and Commu-

nal Hygiene, Moscow, USSR); Pinigin, M. A.; Tarasova, K. I.; Nekrasova, G. I. *Gig Sanit* (12): 27-31; 1977.

The relationship between morphological and functional changes in the liver and the duration of carbon tetrachloride inhalation was studied in albino rats. The extent of liver damage was found to be correlated with duration of exposure. Prolonged exposure (up to 219 days) to a low concentration of CCl<sub>4</sub> (5 mg/m<sup>3</sup>) and short exposure (24 hr) to a high concentration of the carcinogen (300 mg/m<sup>3</sup>) produced similar liver damage. (5 refs)

**78-1431** Persistent Action of Low Doses of Carcinogens on DNA-Synthesis in Comparison with Protein Synthesis in the Regenerating Rat Liver. (Quantitative Autoradiographic Studies). (Eng) Amlacher, E. (Pathologisches Institut, Friedrich-Schiller-Universitat, Jena, Zieglmuhlenweg 1, E. Germany); Danz, M.; Stiller, K. J.; Rudolph, C. *Exp Pathol (Jena)* 14(3/4): 227-231; 1977.

The effects of low doses of carcinogens on DNA and protein synthesis were examined in the regenerating rat liver. Male Wistar rats received carbon tetrachloride (CCl<sub>4</sub>), diethylnitrosamine (DEN), or dimethylbenzanthracene (DMBA) by stomach intubation on six successive days, at a daily dose of 1.5% of the LD<sub>50</sub>. Ten days after the last administration, a two-thirds hepatectomy was performed. The animals received a single ip injection of <sup>3</sup>H-thymidine or <sup>3</sup>H-phenylalanine 24 or 48 hr after the hepatectomy, and they were sacrificed 50 min later. Autoradiography revealed that thymidine incorporation into the liver cells was significantly decreased as a result of the suppressive action of both DENA and DMBA on DNA synthesis. CCl<sub>4</sub> had no effect. The silver grain number over standardized areas of the cyto- and karyoplasm remained unchanged after the administration of <sup>3</sup>H-phenylalanine, indicating that there was no effect on protein synthesis. The <sup>3</sup>H-thymidine labeling index was significantly reduced only following DMBA administration, a finding that was corroborated by liquid scintillation counting. These results indicate that both carcinogens have a suppressive effect on the DNA synthesis rate up to 48 hr after hepatectomy, even when they were applied up to 10 days before the operation. In addition, DMBA also inhibits proliferation, probably by delaying the transition of cells into the growth phase. (22 refs)

**78-1432** Influence of Carbon Tetrachloride on Induction of Tumours of the Liver and Kidneys in Mice by Nitrosamines. (Eng) Pound, A. W. (Dept. Pathology, Univ. Queensland, Brisbane, Australia). *Br J Cancer* 37(1): 67-75; 1978.

Mice were given a single dose of nitrosodimethylamine (DMN), nitrosodiethylamine (DEN), or nitrosomethylamine (MEN), and the yield of liver and kidney tumors



was determined 12 mo later. Nine groups of 50 mice each were given a dose of 0.5 ml/kg carbon tetrachloride (CCl<sub>4</sub>) 24, 48, or 60 hr before injection of 5 mg DMN/kg, 80 mg DEN/kg, or 25 mg MEN/kg, respectively. Other groups of 50 mice each were treated with nitrosamine only or CCl<sub>4</sub> only. DEN was a more potent carcinogen for the liver, and DMN was a more potent carcinogen for the kidney. The susceptibilities of the liver and kidneys were not directly related, since DEN produced more tumors in the liver than DMN or MEN but few in the kidneys. CCl<sub>4</sub>, given 24 or 48 hr before the nitrosamines increased the yields of hepatocellular tumors and proliferative foci in the livers, but not when it was given 60 hr before. This variation of tumor yield with the interval between the doses of CCl<sub>4</sub> and nitrosamine shows that the number of tumors produced is greatest when the carcinogen is given during the period of most active regeneration after the CCl<sub>4</sub> dose. (38 refs)

- 78-1433 Inhibition of (<sup>3</sup>H)Thymidine Incorporation into DNA of Rat Esophageal Epithelium and Related Tissues by Carcinogenic N-Nitroso Compounds.** (Eng) Mirvish, S. S. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Chu, C.; Clayson, D. B. *Cancer Res* 38(2): 458-466; 1978.

The effects of N-nitroso compounds, including several esophageal carcinogens, on (<sup>3</sup>H)thymidine incorporation into the DNA of rat esophageal epithelium was studied. When various doses of eight N-nitroso compounds were injected ip into rats 4 hr before sacrifice, the highest doses inhibited (<sup>3</sup>H)thymidine incorporation by 65%-82%. The dose causing 50% inhibition was 2.3 mg/kg for methyl-n-amylnitrosamine, a specific rat esophageal carcinogen, and 22 mg/kg for the esophageal noncarcinogen, dimethylnitrosamine (DMN). For all eight compounds, the dose causing 50% inhibition was positively correlated with total carcinogenic dose and with total carcinogenic dose per percentage of esophageal tumor incidence, as taken from published experiments. Thymidine incorporation remained inhibited for 2 days after methyl-n-amylnitrosamine injection but < 1 day after DMN injection, and it was inhibited after continuous treatment for 2 wk with methyl-n-amylnitrosamine (2 mg/liter drinking water) or DMN (20 mg/liter). In vivo thymidine incorporation was also inhibited by methyl-n-amylnitrosamine but only at high doses, in the hamster esophagus, hamster trachea, and rat trachea and by N-nitrosopiperidine in the hamster esophagus and trachea. These results correlate positively with organ-specific carcinogenicity in the esophagus but not the trachea, since nitrosamines mainly induce tracheal tumors in the hamster. (40 refs.)

- 78-1434 Some Aspects of Metabolic Activation of Chemical Carcinogens in Relation to Their Or-**

**gan Specificity.** (Eng) Bartsch, H. (International Agency Res. Cancer, Unit Chemical Carcinogenesis, 150 Cours Albert Thomas, F-69008 Lyon, France); Margison, G. P.; Malaveille, C.; Camus, A. M.; Brun, G.; Margison, J. M. *Arch Toxicol (Berl)* 39(1/2): 51-63; 1977.

The role of the organ-specific, enzymic release of alkylating intermediates in determining which tissue develops a tumor in response to a given N-nitrosamine was evaluated on the basis of published data on the carcinogenicity of 62 N-nitrosamines and 21 N-nitrosamides that induce tissue-specific tumors in rats. A good correlation was observed between the metabolic capacity for N-nitrosamine activation and the target organ. A relationship was also noted between the localization of carcinogen-activating enzymes in rat tissues and the site at which a tumor developed following N-(acetoxy)methyl-N-methylnitrosamine administration. The neurotropic carcinogen, 3,3-dimethyl-1-phenyltriazen, which undergoes oxidative N-monodemethylation in the rodent liver to yield the carcinogenic intermediate, 3-methyl-phenyltriazen, causes extrahepatic tumors exclusively. To explain this alternative model of organ specificity, the half-life of 3-methyl-1-phenyltriazen was measured and found to be long enough to permit its distribution throughout the body. Sc injection of 3-<sup>14</sup>C-methyl-1-phenyltriazen into rats yielded alkylated bases in the nucleic acids of hepatic and extrahepatic tissues, including the brain, the major target organ of the parent compound. Thus, for this carcinogen, the persistence of alkylated DNA bases may be a final determinant in tissue-specific tumor induction. (45 refs)

- 78-1435 Formation of Carcinogenic Nitrosamines in Soils.** (Eng) Pancholy, S. K. (Langston Univ., Langston, OK, 73050). *Soil Biol Biochem* 10(1): 27-32; 1977.

The formation of carcinogenic nitrosamines in soils amended with various nitrogenous compounds was examined. Soils amended with nitrite-N and dimethylamine were incubated for 30 days and analyzed every 3 days. Increasing amounts of dimethylnitrosamine were detected up to 12 days. The concentration reached as high as 6.5 ppm, after which there was a decline. Most of the nitrosamines disappeared in soils after 30 days. Addition of inorganic nitrogen reduced the decomposition of dimethylamine. Soil incubation studies with nitrite and trimethylamine showed an 80% reduction in the amount of nitrosamines formed compared to dimethylamine. Analysis of soil samples from fertilized and polluted areas showed significant amounts of nitrate-N but no nitrosamines. Application of 10 ppm of dimethylamine to these soil samples yielded 0.10-0.50 ppm of nitrosamines. Autoclaved soil samples incubated with nitrite and dimethylamine for 12-15 days produced small amounts of nitrosamines. Addition of glucose to the soil samples increased the amounts of nitrosamines formed. The results indicate that nitrosamines were not detected in soils under natural conditions, but the potential for their formation does exist in such an environment. It may not be uncommon to find fairly high



amine concentrations in isolated pockets in soil, particularly as a result of pesticide treatment. (29 refs)

- 78-1436 **The Preferential Formation of Volatile N-Nitrosamines in the Fat of Fried Bacon.** (Eng) Mottram, D. S. (ARC Meat Res. Inst., Langford, Bristol, England); Patterson, R. L.; Edwards, R. A.; Gough, T. A. *J Sci Food Agric* 28(11): 1025-1029; 1977.

Whole bacon slices and the separated lean and fat components were fried and the pan residues and trapped cooking vapors analyzed for N-nitrosopyrrolidine (NPYR) and N-nitrosodimethylamine (NDMA). The fat produced 12 times more NPYR and 6 times more NDMA than the lean, with the largest proportions of both nitrosamines being recovered from the cooking vapors. However, when the bacon was freeze-dried and then cooked in corn oil, the yield of nitrosamines from the lean was many times higher than that produced upon pan frying, but the yield from the fat was not very different. These results indicate that the necessary precursors for nitrosamine formation are present in both fat and lean bacon components, but that higher nitrosamine levels in the fat of pan-fried bacon are due to the nonpolar lipid (80-85% of the adipose tissue), which creates an environment conducive to nitrosamine formation. (13 refs.)

- 78-1437 **Nitrosamine Formation from Interactions of Isosorbide Dinitrate and Hydroxyzine (Meeting Abstract).** (Eng) Raisfeld, I. H. (State Univ. New York Stony Brook, Stony Brook, NY, 11594); Lin, C. *Fed Proc* 37(3): 597; 1978. (no refs)

- 78-1438 **Effect of Dietary Constituents on Nitrosative Toxification of Drugs by Human Salivary Nitrite (Meeting Abstract).** (Eng) Rao, G. S. (Res. Inst., American Dental Assoc. Health Foundation, Chicago, IL); Adatia, M. R. *J Dent Res* 57(A): 245; 1978. (no refs)

- 78-1439 **Mutagenicity Studies on Rats and Mice Given Canned, Heated, Nitrite-Treated Pork.** (Eng) Knudsen, I. (Inst. Toxicology, Natl. Food Inst., 19, Mørkholm Bygade, DK 2860 Søborg, Copenhagen, Denmark); Meyer, D. A. *Mutat Res* 56(2): 177-184; 1977.

Sodium nitrite (200, 1,000, or 4,000 ppm) was added to canned, heated, lean salted (2.5% NaCl) pork and then fed daily to male Wistar/AF/Han/Mol rats for 12 wk and to

male and female Bom/NMRI mice for 8 wk, for the entire period of spermatogenesis. Dominant lethal and heritable translocation tests were then performed. In the latter test, F<sub>1</sub> males were derived from male and female mice fed the nitrite-treated meat for 8 wk before mating. Females were mated to F<sub>1</sub> males and killed and dissected 15 days later. In both rats and mice, there was no significant increase in dominant lethality as a result of the treatment. One F<sub>1</sub> male out of 50 males tested in 4,000-ppm nitrite group was classified as semisterile. This animal had an av of 4.1 living embryos and 60.6% dead implants per female, but there were no histopathological abnormalities in the testes. This finding was not considered significant in view of the number of animals in the experiment. (22 refs)

- 78-1440 **Effects of Imipramine, Nitrite, and Dimethylnitrosamine on Reproduction in Mice.** (Eng) Anderson, L. M. (Walker Lab., Memorial Sloan-Kettering Cancer Center, Rye, NY, 10580); Giner-Sorolla, A.; Ebeling, D.; Budinger, J. M. *Res Commun Chem Pathol Pharmacol* 19(2): 311-327; 1978.

The effects of imipramine (5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride), nitrite, and dimethylnitrosamine (DMN) on the reproductive activity of female CD-1 mice were determined. In a preliminary experiment, mice received 100 mg/kg imipramine in the chow and/or 1 g/liter NaNO<sub>2</sub> in the drinking water or 0.1 ppm DMN in the drinking water. After 10 wk, the mice were mated and treatment was continued. Compared with control (untreated) mice, significantly fewer offspring were weaned in the DMN, imipramine, and nitrite groups. However, this effect was not additive. These experiments were then repeated so that more detailed analyses could be made. Mice receiving imipramine had a significant increase in the percentage of pups dying perinatally, with the majority of these being stillborn. Litters of mice receiving nitrite were the smallest of the three treatment groups, and perinatal death was more common among these mice than among controls. In mice receiving imipramine plus nitrite, 5/20 were judged to be infertile. Of mice that gave birth, perinatal deaths were similar to those in untreated controls. DMN treatment was associated with a doubling of perinatal mortality. Thirty females were then given imipramine and nitrite for 77 days and mated with fertile males. All females became pregnant, and the incidence of perinatal deaths in this group was similar to that in a control group. A biological synergism or in vivo chemical interaction of the two chemicals is suggested. (27 refs)

- 78-1441 **Spermidine Nitrosation and Gastric Cancer (Letter to Editor).** (Eng) Correa, P. (Dept. Pathology, Louisiana State Univ. Medical Center, New Orleans, LA, 70112); Kokatnur, M. G.; Murray, M. L. *Lancet* 1(8059): 324; 1978.



The mutagenicity of spermidine was investigated during its nitrosation in the presence of *Salmonella typhimurium* strain TA1535 at gastric pH levels. When thiocyanate was added, max mutagenesis was observed at pH 3.5-6.0, a range that coincides with that of the gastric juice of patients with advanced atrophic gastritis, a precursor of gastric cancer. Ascorbic acid inhibited mutagenesis when added either before or after the addition of spermidine and nitrite. (4 refs)

- 78-1442 Alterations in Thermal Stability of Rat Liver Chromatin and DNA Induced In Vivo by Dimethylnitrosamine and Diethylnitrosamine.** (Eng) Stewart, B. W. (Sch. Pathology, Univ. New South Wales, P.O. Box 1, Kensington, New South Wales 2033, Australia); Farber, E. *Cancer Res* 38(3): 26-31; 1978.

The effects of in vivo exposure of male Wistar rats to dimethylnitrosamine (DMN) and diethylnitrosamine (DENA) on the transition temperature ( $T_m$ ) of sheared chromatin and DNA isolated from the liver were studied.  $^3H$ -thymidine was given after partial hepatectomy, and DMN or DENA was injected ip after at least a 2-wk recovery period. Animals were killed at various times after treatment. Analysis of the chromatin and DNA was made by thermal chromatography on hydroxyapatite, and the elution profile was followed during the operation of a continuous temperature gradient. With a nonnecrogenic dose of DMN (10 mg/kg), the alterations in chromatin were maximal at 24 hr and had disappeared by 3 days. Greatest differences in elution profiles of chromatin after DMN treatment were observed in the region above 80 C. Administration of DMN caused a lowering of the melting curve in this region, the displacement from control position being proportional to the dose. The maximum dose (60 mg/kg) displaced the complete chromatin melting curve up to 5 C to the lower side. DNA isolated from this chromatin melted 3 C less than that from control rats. Administration of lower doses of DMN did not affect the melting profile of DNA. Similar results were observed with DENA, but the modification was also seen at 50-60 C. These results, in which variation in the properties of chromatin are demonstrable in the absence of analogous changes in DNA, imply that the nature of DMN- or DENA-induced changes to genetic material cannot be fully described in terms of DNA chemistry alone. (48 refs)

- 78-1443 Inhibition of Diethylnitrosamine (DEN) Induced Acute Liver Cell Necrosis by Diethyldithiocarbamate (DEDTC): A Possible Site of Action After the Activation Step (Meeting Abstract).** (Eng) Ying, T. S. (Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada); Sarma, D. S.; Farber, E. *Fed Proc* 37(3): 402; 1978. (no refs)

- 78-1444 Regulation of Glucose-6-phosphate Metabolism in Hepatocarcinogenesis and in Hepatoma.** (Rus) Birk, R. V. (Inst. Experimental and Clinical Medicine, Tallin, USSR). *Vestn Akad Med Nauk SSSR* (10): 84-87; 1977.

The activity and isozyme spectra of glucose-6-phosphate dehydrogenase (G-6-PDH) were assessed in the liver and hepatoma tissue of C3HA mice. The tumors were induced by diethylnitrosamine (DENA) administered in the drinking water (2.5 mg/kg, 6x/wk). The first hepatomas and multiple foci of hyperplasia appeared 6 mo after the initiation of the experiment. Hepatic G-6-PDH activity started to increase within 3-4 mo of DENA administration, and it reached a maximum in the primary hepatoma tissue. The characteristic feature of the enzyme spectrum in the hepatoma was a marked elevation of isozyme I activity (32.1%, compared with 7.5% in controls). (10 refs.)

- 78-1445 Modification of Chemical Carcinogenesis with Adrenergic Compounds.** (Rus) Gurkalo, V. I. (N. N. Petrov Scientific Res. Inst. Oncology, Leningrad, USSR); Zabezhinsky, M. A. *Vestn Akad Med Nauk SSSR* (2): 38-42; 1978.

The effect of various adrenergic agents (agonists and antagonists) on diethylnitrosamine (DENA)-induced blastomogenic transformation in the liver and esophagus was evaluated in random-bred albino mice. The mice were fed DENA in the drinking water for 4 mo (total dose 90-95 mg) plus (Group 1) noradrenaline (2.5 mg/kg) and pyrrhoxane (25 mg/kg) (Group 2) butyroxane (25 mg/kg) and atropine, and (Group 3) isoproterenol (0.1 mg/kg) and its antagonist obzidan (1 mg/kg). Adrenergics were given in sc injections, 3x/wk for 4 mo together with DENA and then for 2 mo after termination of DENA administration. The surviving rats were sacrificed, and the histological changes in the liver and esophagus were analyzed. DENA alone induced hepatocellular carcinoma in 29%-74% of the animals; noradrenaline and atropine enhanced hepatocarcinogenesis (60% and 85% of the respective rats developed liver carcinoma), but isoprenaline inhibited it (14% incidence). Cholinolytic adrenaline in combination with DENA was found to induce the esophageal tumors: 46% of the animals developed squamous cell carcinoma of the esophagus. (14 refs)

- 78-1446 Oncogenic Effects of Diethylnitrosamine in the Rat Liver: Biochemical and Morphological Observations (Meeting Abstract).** (Eng) Giuliani, E. R. (Rutgers Univ., Newark, NJ, 07102); Hall, J. C.; Zaki, F. G. *Fed Proc* 37(3): 597; 1978. (no refs)



1447 **Diethylnitrosamine-induced Changes in the Nuclear Fraction Ratios in Rat Liver Cells.** (Ukr) Achishin, V. P. (Inst. Problems in Oncology, Kiev, URSS); Bikoriz, A. I.; Shumilina, V. V. *Dopov Akad Nauk RSR [Ser B]* (11): 1017-1020; 1977.

dom-bred albino rats were inoculated with a single dose of diethylnitrosamine (DENA: 100 mg/kg, ip); 12 hr and 1, 7, and 14 days later, the animals were sacrificed and the DNA content in the isolated liver nuclei was assessed. On day 2 after injection, 78% of the hepatocytes had a diploid DNA content (diploid:tetraploid cells ratio was 3.6, compared with 1.78 in control rats). After day 2, the number of tetraploid cells showed a progressive increase, and 7 days after DENA injection the diploid:tetraploid cell ratio was 1.3. (13 refs)

1448 **The In Vivo Induction of Sister Chromatid Exchanges in the Bone Marrow of the Chinese Hamster. II. N-Nitrosodiethylamine (DEN) and N-propyl- $\alpha$ -(2-methylhydrazino)-p-toluamide (Natulan), Carcinogenic Compounds with Specific Mutagenicity Problems.** (Eng) Bayer, U. (Forstbotanisches Institut der Universität, Freiburg im Breisgau, W.Germany). *Mutat Res* (1): 305-309; 1978.

ability of N-nitrosodiethylamine (DEN) and N-propyl- $\alpha$ -(2-methylhydrazino)-p-toluamide (Natulan) to induce sister chromatid exchanges (SCE) was determined in Chinese hamsters. DEN was injected ip at doses of 10, 50, 100, and 200 mg/kg, and Natulan was injected ip at doses of 10, 25, 50, 100, 200, and 300 mg/kg; the animals were sacrificed 24 hr later. At the two highest doses, DEN induced a slight increase in SCE frequency, compared with controls, but the increase was not significant. For Natulan, there was a clear dose-response relationship: the increase in SCE became significant between doses of 10 and 25 mg/kg, and the number of SCE reached a plateau between 200-300 mg/kg. The shape of the curve was thus similar to that observed for hydrocarbons. A review of the literature revealed that DEN induces point mutations at the molecular level in microorganisms and *Drosophila*, but Natulan gives positive results with in vivo mammalian tests and negative results with microorganisms. It is suggested that in vivo SCE tests be used with mutagenicity tests in evaluating a chemical for carcinogenicity. In a repeat of the DEN experiment using larger cell numbers, a significant increase in the number of SCE was observed at the 100- and 200-mg/kg doses. (19 refs)

1449 **Alpha-Hydroxylation in the Metabolism of N-Nitrosopiperidine by Rat Liver Microsomes: Formation of 5-Hydroxypentanal.** (Eng) Leung, K. H. (Dept.

Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Park, K. K.; Archer, M. C. *Res Commun Chem Pathol Pharmacol* 19(2): 201-211; 1978.

The metabolism of N-nitrosopiperidine (NNP) was examined using the S-9 fraction from phenobarbital-induced (1 g/liter in the drinking water for 7 days) male albino Sprague-Dawley rat liver. NNP was metabolized to 5-hydroxypentanal (mainly the cyclic form). This finding indicates that one pathway in the microsomal oxidation of NNP is oxidation at the carbon atom alpha to the N-nitroso group. This mechanism parallels the postulated metabolic pathway for production of the ultimate carcinogen from simple dialkyl nitrosamines. Oxidations at positions other than the alpha carbon atom probably do not represent metabolites that lead to the production of ultimate carcinogens. (13 refs)

78-1450 **Effect of FT-207 on Rat Urinary Bladder Tumors Induced by N-Butyl-N-(4-hydroxybutyl) nitrosamine. I. Effect of Intraperitoneal Administration of FT-207 on Development of Urinary Bladder Tumors.** (Jpn) Okajima, E. (Dept. Urology, Nara Medical Univ., Kashiwara-shi, Nara Prefecture 634, Japan); Motomiya, Y.; Ijuin, M.; Hijioka, T.; Ohara, S.; Shiomi, T.; Babaya, K.; Tanaka, M.; Maruyama, Y. *Cancer and Chemotherapy* 4(4): 805-811; 1977.

Of 13 Wistar rats given 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) in their drinking water for 8 wk, 92% developed tumors. BBN-induced changes in the urinary bladder included cancer (23.1%), hyperplasia (100%), papilloma (69.2%), and metaplasia (23.1%). When BBN-treated rats were divided into three groups and treated with N<sub>1</sub>-(2-tetrahydrofuryl)-5-fluorouracil (FT-207: 100 mg/kg/day) for 7 consecutive days after BBN administration (Group A, 29 animals), 7 consecutive days every 2 wk (Group B, 14 animals), or weekly for 12 wk (Group C, 12 animals), tumor incidence was 48.3%, 42.9%, and 41.7%, respectively. Although 10.3% of Group A and 8.3% of Group C animals had bladder cancer, Group B rats had no malignant tumors. The results demonstrate that FT-207 can significantly inhibit bladder tumor formation by BBN. (18 refs)

78-1451 **Heritable Membrane Alterations and Growth Associated with Enhanced Leupeptin-sensitive Proteinase Activity in Epithelial Cells Exposed to Dibutyl nitrosamine In Vitro.** (Eng) Pietras, R. J. (Dept. Biology, Univ. California, Los Angeles, CA, 90024). *Cancer Res* 38(4): 1019-1030; 1978.

Early changes in male bullfrog (*Rana catesbeiana*) and male New Zealand white rabbit urinary bladder epithelium were



examined following in vitro treatment with varying amounts of dibutyl nitrosamine (DBN) and the noncarcinogen diphenyl nitrosamine (DPN). At  $5 \times 10^{-4}$  M DBN, there were max increments in labeled thymidine incorporation and growth in cells maintained in serum-free, chemically defined medium, compared with control cells and cells treated with DPN. The DBN-induced effects were abolished by prior treatment of cells with liposome-entrapped leupeptin and were reduced by ovomucoid, but not by soybean trypsin inhibitor. Extracellular release of cathepsin B1 activity was enhanced to 280% of that of control cells within 1 hr of DBN treatment. Concanavalin A (Con A)-mediated binding of RBC, but not Con A binding, to bullfrog cells increased to 194% of the level in cells treated for 1 hr with DPN. Furthermore, fluorescence microscopy indicated that 20% of the cells exposed to DBN showed a clustering of Con A-binding sites that are normally distributed at random on the external cell surface. Inter cellular adhesion was also enhanced following DBN treatment. The DBN-induced membrane alterations were diminished by treatment with cathepsin B1 inhibitors and were propagated during 14-day culture after the initial DBN exposure. Fractionation of cells by selection for enhanced adhesiveness due to DBN exposure for 30 min elicited a rapidly dividing cell fraction active in cathepsin B1 secretion, compared with their less adhesive counterparts. Thus, the heritable membrane alterations and enhanced cell growth induced by DBN are associated with increases in the activity of a leupeptin-sensitive proteinase at the external cell surface. (59 refs)

**78-1452 Carcinogenic Effect of N-Bis(2-hydroxypropyl)nitrosamine by Oral Administration in Mice.** (Eng) Konishi, Y. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijocho Kashihara, Nara 634, Japan); Kondo, H.; Inui, S.; Denda, A.; Ikeda, T.; Kojima, K. *Cancer Lett* 3(5/6): 255-257; 1977.

2,2'-Bis(hydroxypropyl)nitrosamine (BHP) was inserted in the drinking water of several groups of dd strain male mice at doses of (1) 0 (controls), (2) 100, (3) 250, (4) 500, and (5) 1,000 ppm, and its carcinogenicity was evaluated. The intake of BHP per animal was 0, 6.3, 13.9, 22.4, and 34.2 mg/day, respectively. The av initial wt of the mice was 19 g in Groups 1-4, 40 g in Group 5. At sacrifice 16 wk later, the body wts for Groups 1-5 were 38, 32, 21, 24, and 31 g, respectively. The main targets for the carcinogenic effect of BHP were the lung and liver ( $p < 0.001$ ). The respective lung tumor incidence for the five groups was 0/18, 10/11, 9/11, 8/11, and 8/14 mice; the respective liver tumor incidence was 0/18, 8/11, 8/11, 8/11, and 14/14. The lung tumors were multiple, 2- to 3-mm-diameter, glossy whitish nodules located on the surface. Histologically, they were alveogenic adenomas with occasional areas of atypia or adenocarcinomas (4 mice); no metastases were found. The liver showed vascular tumors that were cavernous hemangiomas, hemangioendotheliomas (11 animals, Groups 4 and 5 only), and hemangioendotheli-

osarcomas (3 animals, Group 5 only). Metastasis, into cervical lymph node, was observed in only one mouse. These results, and those of previous studies in which BHP caused high incidences of pancreatic duct tumors in sc treated Syrian hamsters, support the view that the carcinogenicity of nitrosamine compounds is influenced by their chemical properties and tissue- and species-specific factors. (8 refs.)

**78-1453 Metabolism of the Radiolabeled Pancreatic Carcinogens N-Nitrosobis(2-oxopropyl)amine and N-Nitrosobis(2-hydroxypropyl)amine in Hamsters (Meeting Abstract).** (Eng) Gingell, R. (Eppley Inst. Res. Cancer, 42nd and Dewey, Omaha, NB, 68105); Brunk, Kupper, R. *Proc Am Assoc Cancer Res* 19: 188; 1978. (no refs)

**78-1454 The Effects of DIPN on Organ-Cultured Embryonic Rat Pancreas (Meeting Abstract).** (Eng) Parsa, I. (State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203); Sonchai, P. *Fed Proc* 37(3): 232; 1978. (no refs)

**78-1455 Enzymological and Histochemical Study of Early Stages of Carcinogenesis in Peripheral Nervous System of the Rat.** (Rus) Kolodin, V. I. (Lab. Experimental Tumors, N. N. Petrov Scientific Res. Inst. Cytology, Leningrad, USSR). *Vopr Onkol* 23(11): 79-88; 1977.

Albino random-bred pregnant rats were inoculated with nitroso-N-ethylurea (NEU: 40 mg/kg, ip). The 1- to 5-old offspring of the exposed rats were sacrificed, and trigeminal and acoustic nerves were examined enzymologically and histochemically. The first blastomatous changes in the trigeminal nerves were detected in 14-day-old rats. The characteristic features of the early stages of NEU-induced transplacental carcinogenesis included Schwann cell proliferation, increased activity of the enzymes of the pentose phosphate cycle, glycolysis and hydrolysis of  $\alpha$ -phosphoric carbonic acid esters, and decreased activity of monoamine oxidase, succinate dehydrogenase, malate dehydrogenase, NAD, and NADP. The first tumors of the peripheral nervous system started to appear in 6-mo-old rats. Since the enzyme profile of the neurinomas was similar to that in proliferating glial cells, it was concluded that malignant transformation of glial cells preceded the clinical manifestations of tumor growth. (27 refs)

**78-1456 Selective Accumulation of O<sup>6</sup>-Methylguanine DNA of Rat Bladder Epithelium after Intravascular**



**Administration of N-Methyl-N-nitrosourea.** (Eng) Cox, Cancer Res. Lab., Veterans Admin. Hosp., Memphis, 38104; Irving, C. C. *Cancer Lett* 3(5/6): 265-270; 1977.

amounts of 7-methylguanine, O<sup>6</sup>-methylguanine (O<sup>6</sup>-MG), and 3-methyladenine in the DNA of female Wistar rat bladder epithelium were determined after the intravesical administration of single and multiple weekly doses of 0.5 mg methyl-N-nitrosourea (MNU). After a single dose of MNU, O<sup>6</sup>-MG was removed from the DNA at slower rates than the other two compounds. 3-Methyladenine was not detected in the bladder epithelium DNA after two or four doses; however, the amount of O<sup>6</sup>-MG after four doses was twice that found following a single dose. Levels of 7-methylguanine remained the same after 1, 2, or 4 doses. The rate of excision of O<sup>6</sup>-MG and the accumulation of this product in DNA following MNU treatment correlate with the ability of MNU to induce bladder tumors. Similar findings were found in the literature for brain tissue, another target of MNU carcinogenesis. (10 refs)

**4457 N-Methyl-N-nitrosourea (MNU)-induction of Tracheal Cancer--A Respiratory Cancer Model with a Short Latency Period (Meeting Abstract).** (Eng) Becci, J. (IIT Res. Inst., Chicago, IL, 60616); Grubbs, C. J.; Thompson, H. J.; Dooley, L.; Moon, R. C. *Fed Proc* 37(3): 261; 1978. (no refs)

**4458 Carcinogenicity of a Methyl-Nitrosourea Amino Acid in Rats (Meeting Abstract).** (Eng) Longmeyer, D. S. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH, 03755); Curphey, T. J.; Lilja, H. S.; French, J. L.; Daniel, D. S. *Fed Proc* 37(3): 231; 1978. (no refs)

**4459 Pathogenesis of Tracheal Carcinoma Induced by N-Methyl-N-nitrosourea (MNU) in Hamsters (Meeting Abstract).** (Eng) Stinson, S. F. (Lung Cancer Branch, NCI, Bethesda, MD, 20014); Sporn, M. B. *Proc Am Soc Cancer Res* 19: 192; 1978. (no refs)

**4460 Change in Epidermal Chalone Activity in Response to Exposure to Carcinogen and Epilation (Rus) Ketlinskii, S. A.** (Lab. Experimental Histology, Experimental Medicine, Leningrad, USSR); Okulov, V. *Biull Eksp Biol Med* 85(3): 354-356; 1978.

role of epidermal chalones in tissue regeneration was studied in random-bred rats and C57BL mice. Rats were divided into two groups: group 1 received a single topical ap-

plication of methyl-Nitrosourea (MNU), Group 2 was subjected to epilation of the corresponding skin region; 1, 2, 3, 5, and 12 days later, the rats were sacrificed. The chalones extracted from the skin of both groups were injected (0.5 mg, ip) into the mice; 4 hr later, the mice were sacrificed and the mitotic activity in the ear epidermis was assessed. Injection of chalones derived from control (untreated) rats resulted in significant (89%) inhibition of mitotic activity in the ear epidermis. Exposure to the carcinogen or epilation resulted in marked decrease in the inhibitory activity of the chalones: the mitotic activity in mice inoculated with chalones extracted within 1-2 days of MNU administration and within 1 day of epilation did not differ from the mitotic activity in control mice. It is suggested that the temporary inactivation of the chalones from Group 1 rats was due to the toxic effect of the carcinogen on protein synthesis; the inactivation of the chalones from Group 2 rats was consistent with the hypothesis that proliferating cells lose their ability to synthesize chalones. (10 refs)

**78-1461 Effect of Retinoids on N-Methyl-N-nitrosourea (MNU)-induced Mammary Cancer (Meeting Abstract).** (Eng) Thompson, H. J. (IIT Res. Inst., Chicago, IL, 60616); Grubbs, C. J.; Becci, P. J.; Sporn, M. B.; Moon, R. C. *Fed Proc* 37(3): 261; 1978. (no refs)

**78-1462 Induction of Dominant-Lethal Mutations After Administration of Ethylenethiourea in Combination with Nitrite or of N-Nitroso-Ethylenethiourea in Mice.** (Eng) Teramoto, S. (Inst. Environmental Toxicology, 2-772, Suzuki-cho, Kodaira-shi, Tokyo 187, Japan); Shingu, A.; Shirasu, Y. *Mutat Res* 56(3): 335-340; 1978.

The mutagenic potentials of ethylenethiourea (ETU) and/or sodium nitrite and of N-nitroso-ETU were investigated using the mouse dominant-lethal test. Male C3H/HeCr mice were treated po for 5 days with ETU (0, 30, or 150 mg/kg/day) and/or sodium nitrite (0, 10, or 50 mg/kg/day) or N-nitroso-ETU (100 mg/kg/day). The mice were then mated to untreated females. The simultaneous administration of ETU (150 mg/kg) and sodium nitrite (50 mg/kg) caused a significant decrease in the percentage of pregnancies ( $p < 0.001$ ) at week 6 and a significant decrease in the number of fertilized eggs at weeks 5 and 6 ( $p < 0.05$  and  $p < 0.001$ , respectively). These effects were not seen when the chemicals were administered separately. No dominant-lethal mutations were induced in animals treated with 30 mg/kg ETU plus 10 mg/kg sodium nitrite. The administration of N-nitroso-ETU caused a significant reduction in the number of pregnancies at week 6 ( $p < 0.001$ ) and in the number of live embryos per pregnancy at weeks 4 and 6 ( $p < 0.05$ ). The results indicate that mutagenic alterations might be induced in mouse germ cells by the interaction of sodium nitrite with ETU. (14 refs)



- 78-1463 Effect of Toxic Thioureas on Resistance of Rats to Growth in the Lungs of Intravenously and Intratracheally Seeded Tumour Cells.** (Eng) van den Brenk, H. A. (64 Kooyong Road, Armadale, Victoria 3143, Australia); Kelly, H.; Holland, K. L. *Br J Cancer* 37(1): 92-104; 1978.

Clonogenic growth (colony-forming efficiency, CFE) of iv injected allogeneic W256 tumor cells in the lungs was markedly enhanced by treatment of female rats with  $\alpha$ -naphthylthiourea (ANTU) injected ip from 2 hr before to 2 hr after the tumor cells. ANTU specifically increases pulmonary vascular permeability in adult rats and causes acute pulmonary edema and pleural effusion. Inhibition of drug toxicity to the lungs by tachyphylaxis, specific antimetabolites, or iodides did not abolish the effect of ANTU on CFE. CFE was not increased when cells were seeded by iv injection in lungs affected by advanced pulmonary edema at 6-24 hr after ANTU treatment. ANTU did not enhance the growth of intratracheally injected cells. Treatment of tumor-immunized rats with ANTU caused an apparent breakdown of tumor immunity in 50% of rats by causing growth of tumor colonies in the lungs. These results indicate that enhancement of CFE does not appear to depend simply on the presence and degree of pulmonary edema. This effect may depend on some perturbation of pulmonary physiology, eg, a perturbation of cyclic nucleotide metabolism, which may also be the primary event on which the production of increased capillary permeability depends. (18 refs)

- 78-1464 Effect of Various Dietary Fibers and Food Additives on Azoxymethane (AOM) or Methylnitrosourea (MNU)-induced Colon Carcinogenesis in Rats** (Meeting Abstract). (Eng) Watanabe, K. (American Health Foundation, Valhalla, NY, 10595); Reddy, B. S.; Kritchevsky, D. *Fed Proc* 37(3): 262; 1978. (no refs)

- 78-1465 Trophic and Co-carcinogenic Actions of Pancreaticobiliary Secretions** (Meeting Abstract). (Eng) Williamson, R. C. (Dept. Surgery, Univ. Bristol, Bristol, England); Bauer, F. L.; Ross, J. S.; Malt, R. A. *Isr J Med Sci* 146(Suppl 1): 8; 1977. (1 ref)

- 78-1466 The Cytochemical Demonstration of  $\beta$ -Glucuronidase in Colon Neoplasms of Rats Exposed to Azoxymethane.** (Eng) Brown, C. A. (Carcinogen Metabolism and Toxicology Branch, NCI, NIH, Bethesda, MD, 20014). *J Histochem Cytochem* 26(1): 22-27; 1978.

$\beta$ -Glucuronidase patterns were studied in preneoplastic and neoplastic colons of male Fischer rats given 10 weekly sc injections of 7.4 mg/kg azoxymethane for 4 or 7 mo. Poly-

poid lesions, adenocarcinomas, and mucinous adenocarcinomas were induced in the area of Peyer's patches (which also showed lymphoid aggregation) and throughout the colon. Enzyme activity was detected in the cytoplasm of columnar epithelial cells along the intestinal tract, the epithelial cells lining the lymphoid sinuses, and the postcapillary venules of small intestine, the colon of control rats, and normal areas of colon from rats given azoxymethane. The enzyme staining reaction was more intense in tumor areas mainly in the stroma of the tumor. Crypts along a tumor area with an intact tunica muscularis mucosa had little enzyme activity; activity in the glandular structures and crypts was seen only in nonmalignant areas with a discontinuous tunica muscularis. Crypts undergoing transformation showed a definite increase in  $\beta$ -glucuronidase. Differences in enzyme activity for polyoid lesions, adenocarcinomas, and mucinous adenocarcinomas were not striking. Few tumors metastasized to lymph nodes, and those that did showed no significant difference in enzyme patterns. This technique can be used to detect neoplastic transformation. (22 refs)

- 78-1467 Damage and Repair in DNA of Bone Marrow and Spleen of Rats Induced by Methylazoxymethanol Acetate** (Meeting Abstract). (Eng) Preston, A. (Univ. Puerto Rico Sch. Medicine, San Juan, PR, 00931); Roman Franco, A. A.; El Khatib, S. M. *Fed Proc* 37(3): 4; 1978. (no refs)

- 78-1468 Mutagenicity of Heterocyclic Nitrogen Mustards (ICR Compounds) in Cultured Mammalian Cells.** (Eng) O'Neill, J. P. (Univ. Tennessee, Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37831); Fuscoe, J. C.; Hsie, A. W. *Cancer Res* 38(3): 22-25; 1978.

The mutagenicity of six heterocyclic nitrogen mustards (ICR compounds) was determined in a cultured mammalian system using resistance to the purine analog 6-thioguanine to select for mutation induction at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus in Chinese hamster ovary cells. The six compounds tested were ICR 170, 292, 372, 191-OH, and 170-OH. ICR 191 and 170 contain the same heterocyclic nucleus (the methoxyacridine series) but have slight side-chain differences, 191 being a secondary and 170 a tertiary amine. ICR 372, an azaacridine, has a different nucleus but the same secondary amine side chain as 191, and 292 has a benz(a)acridine nucleus and same tertiary amine side chain as 170. All four contain a single 2-chloroethyl group (nitrogen half-mustard) on the side chain and are mutagenic. ICR 170 and 292 were 10 to five times more mutagenic than ICR 191 and 372. The 191-OH and 171-OH derivatives, in which the 2-chloroethyl group is replaced by a hydroxyl group, were not mutagenic. These results indicate that the 2-chloroethyl group is needed for mutation induction. (13 refs)



69  **$\beta$ -Glucuronidase and the Gastric Epithelial Cell: A Study Using Organ Culture.** (Eng) Taylor (Dept. Medicine, Univ. Sydney at Royal North Shore, St. Leonards, New South Wales 2065, Australia); Orr, R. L.; Piper, D. W. *Digestion* 16(1/2): 40-47; 1978.

Significance of increased  $\beta$ -glucuronidase levels in the gastric juice of patients with gastric carcinoma was studied by exposing organ cultures of gastric mucosa from cancer or benign peptic ulcer patients to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.75 mM) or to the cytotoxic agent nitrogen mustard (NM: 50  $\mu$ g/ml). The response to each agent was monitored by measuring the viability of the gastric mucosal cells,  $\beta$ -glucuronidase and lactic acid production in the ambient fluid, and changes in the lactic dehydrogenase isoenzyme patterns of the tissue homogenates. MNNG significantly increased  $\beta$ -glucuronidase and lactic acid production by the mucosal cells of both patient and control strains. NM decreased this production, indicating that the response to MNNG was not due to cell necrosis. Thus, changes in gastric juice  $\beta$ -glucuronidase activity may be indicative of malignancy. (35 refs.)

70 **Correlation of Anchorage-independent Growth with Tumorigenicity of Chemically Transformed Mouse Epidermal Cells.** (Eng) Colburn, N. H. (Dept. Environmental Industrial Health, Univ. Michigan, Ann Arbor, MI, 48109); Bruegge, W. F.; Bates, J. R.; Gray, R. H.; Smith, J. D.; Kelsey, W. H.; Shimada, T. *Cancer Res* 38(3): 434; 1978.

Primary cultures of BALB/c mouse epidermal cells were transformed with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 1-2  $\mu$ g/ml) at 0-3 days postplating, followed in some cases by treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA:  $5 \times 10^{-6}$  M). After 3-4 mo, the cultures yielded morphologically altered cell strains, three of which were tumorigenic when injected into syngeneic newborn mice. One control culture yielded a tumorigenic strain, but two other controls (dimethyl sulfoxide or acetone) gave rise to non-tumorigenic strains. All strains examined by electron microscopy showed intermediate junctions, an epithelial morphology, and a morphological feature distinguished tumorigenic from non-tumorigenic strains. Although the tumorigenic strains appeared to have a shorter doubling time, rapid growth in primary culture did not always parallel tumorigenicity. In soft agar, colony formation in 0.33% agar medium consistently correlated with tumorigenicity. Cell strains showing tumorigenicity and/or growth in soft agar arose after MNNG or MNNG + repeated TPA treatment, indicating that exposure to a tumor promoter is not necessary for the expression of neoplasia initiated by a chemical carcinogen. (54 refs)

71 **Induction of Premalignant and Malignant Changes in Normal Human Prostate by N-**

**Methyl-N'-nitro-N-nitrosoguanidine (MNNG) in Organ Culture (Meeting Abstract).** (Eng) Sanefuji, H. (Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201); Trump, B. F.; Mostofi, F. K.; Schiffer, C. A. *Proc Am Assoc Cancer Res* 19: 223; 1978. (no refs)

78-1472 **Evaluation of Genetic Risks of Alkylating Agents. IV. Quantitative Determination of Alkylated Amino Acids in Haemoglobin as a Measure of the Dose after Treatment of Mice with Methyl Methanesulfonate.** (Eng) Segerback, D. (Dept. Radiology, Wallenberg Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden); Calleman, C. J.; Ehrenberg, L.; Lofroth, G.; Osterman-Golkar, S. *Mutat Res* 49(1): 71-82; 1978.

The use of specific amino acids in Hb for determining the tissue dosimetry of alkylating agents was investigated using methyl methanesulfonate (MMS) as a model compound. Following ip injection of 0.54, 11, and 132 mg/kg MMS into male CBA mice, the degree of Hb alkylation exhibited a linear dependence on the quantity of MMS injected. The degree of alkylation of guanine-N-7 in DNA indicated a slight positive deviation from linearity at high doses. Following a single MMS injection, the degree of alkylation of cysteine-S and histidine-N-3 in Hb decreased linearly with time, reaching zero after approx 40 days (lifetime of RBC in mice). In a second experiment, mice received 19 mg/kg MMS once a week for 8 wk; there was an accumulation of alkylated groups in the Hb, as expected. A gas chromatographic method for the quantitative determination of S-methylcysteine in a protein hydrolysate is presented. (19 refs)

78-1473 **DNA Repair in Normal and Preneoplastic Mammary Tissues.** (Eng) Bodell, W. J. (Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720); Banerjee, M. R. *Cancer Res* 38(3): 736-740; 1978.

DNA repair in hormone-dependent normal mammary tissue was compared with that in hormone-independent preneoplastic D<sub>1</sub>-hyperplastic alveolar nodule (HAN) outgrowths from BALB/c mice after treatment with 3 nanomoles (nmol) methyl methanesulfonate (MMS). Preliminary studies in which cells were exposed to 5 nmol hydroxyurea (HU) alone indicated that 98% of the semiconservative DNA replication is inhibited by this treatment. Treatment of mammary gland fragments with HU + MMS resulted in a four- to sevenfold higher incorporation of labeled thymidine into cell DNA than HU treatment alone. In both D<sub>1</sub>-HAN and normal mammary tissue, this incorporation represented DNA repair replication; similar levels of repair replication were found in both tissue types. DNA repair synthesis occurred in 30%-50% of both mammary gland and D<sub>1</sub>-HAN outgrowth epithelial cells; no synthesis was observed in fat or stromal cells from the mammary glands. However, the labeling index was not uniform throughout all tissues. These results suggest that



a reduced DNA repair capacity is not associated with the increased sensitivity of D<sub>1</sub>-HAN outgrowths to the tumorigenic effect of carcinogens. (49 refs)

**78-1474 Enhancement of Carcinogen-induced Mutagenesis in Rat Liver Epithelial Cultures Enriched in S Phase Cells (Meeting Abstract).** (Eng) Tong, C. (Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595); Williams, G. M. *Fed Proc* 37(3): 750; 1978. (no refs)

**78-1475 Sister Chromatid Exchange as an Indicator of Mutagenesis.** (Eng) Carrano, A. V. (Biomedical Div., L-452, Lawrence Livermore Lab., Livermore, CA, 94550); Thompson, L. H.; Lindl, P. A.; Minkler, J. L. *Nature* 271(5645): 551-553; 1978.

The relationship between sister chromatid exchanges (SCE) and mutagenesis was investigated in a Chinese hamster ovary cell line using ethylmethane sulfonate (EMS;  $0.2 \times 10^3$  M), N-ethyl-N-nitrosourea (ENU;  $0.2 \times 10^3$  M), mitomycin C (MMC;  $0.75 \times 10^6$  M), and proflavine sulfate (PRO;  $0.15 \times 10^6$  M). EMS, ENU, and MMC produced a linear increase in both mutations producing 8-azaguanine resistance and SCE as a function of dose; PRO did not produce a significant increase in either. However, for comparison with other chemicals, all data were interpreted as producing positive results. On a molarity basis, both SCE and mutations thus increased over four orders of magnitude as follows: EMS < ENU < PRO < MMC. There was a linear relation between SCE and mutations, but the ratio of SCE to mutations was different for each compound. ENU had the lowest ratio, MMC the highest. For the approx 50,000 structural genes in man, these data suggest that for every SCE per cell EMS produces 0.85 mutation/cell, ENU produces 1.2 mutations, PRO produces 0.28 mutation, and MMC produces 0.08 mutation. (19 refs)

**78-1476 Mutagenicities of the Pyrolyzates of Peptides and Proteins.** (Eng) Matsumoto, T. (Central Res. Inst., Japan Tobacco and Salt Public Corporation, 6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan); Yoshida, D.; Mizusaki, S.; Okamoto, H. *Mutat Res* 56(3): 281-288; 1978.

The pyrolyzates of 10 peptides, 10 proteins, and 5 naturally occurring materials were tested for mutagenicity in the histidine-requiring mutants *Salmonella typhimurium* TA98 and TA100. The peptides used were Gly-Gly, Gly-L-Glu, Gly-L-Pro, L-carnosine, DL-Leu-Gly-DL-Phe, L-Try-L-Try, Gly-L-Try, L-Try-Gly, L-Try-L-Ala, and L-Try-L-Try. The proteins used were ovalbumin, collagen, casein, histone, insulin, lysozyme, zein, gluten, fraction 1 protein, and tobacco pro-

tein. The naturally occurring materials were fresh meat, fish and tobacco leaves. The pyrolyzates of the peptides and proteins gave negative results in the absence of S-9 mix in both strains, indicating that mutagens present in the pyrolyzate required S-9 mix for metabolic activation. Significant mutagenic activities were detected, in the presence of the S-9 mix, in the pyrolyzates of all peptides and proteins except Gly-Gly. The pyrolyzates of peptides containing tryptophan showed especially high mutagenicity, indicating that tryptophan contributed to this mutagenicity. The mutagenicity of the naturally occurring products increased almost linearly with dose when assayed in the presence of the S-9 mix. The pyrolyzate of the tobacco leaf protein also showed mutagenicity. The higher the protein content in the leaf, the higher the mutagenicity of the pyrolyzate. Tobacco leaf protein may be the principal precursor of mutagens in tobacco smoke condensates. (16 refs)

**78-1477 The Efficiency and Extent of Mutagenic Activity of Some New Mutagens of Base-Analog Type.** (Eng) Janion, C. (Inst. Biochemistry and Biophysics, Polish Acad. Sciences, Rakowiecka 36, 02-532 Warsaw, Poland). *Mutat Res* 56(3): 225-234; 1978.

N<sup>4</sup>-Hydroxycytidine, 5-methyl-N<sup>4</sup>-hydroxydeoxycytidine and 2-amino-N<sup>6</sup>-hydroxyadenine were tested for mutagenicity in *Salmonella typhimurium* and *Escherichia coli*. 2-Amino-N<sup>6</sup>-hydroxyadenine was the most potent mutagen, giving more than 1,000 colonies of revertants per plate in several cases. N<sup>6</sup>-Hydroxycytidine was the least specific mutagen. Almost all the tested markers were reverted by this analog. The mutagenic potency of 5-methyl-N<sup>4</sup>-hydroxydeoxycytidine was in the same range as that of 2-aminopurine, but the specificities of the two compounds seemed to be opposite in action. Since 2-aminopurine leads to AT-GC transitions, it is probable that 5-methyl-N<sup>4</sup>-hydroxydeoxycytidine can induce the transition of CG to TA. A comparison of the mutagenic actions of N<sup>4</sup>-hydroxycytidine and 5-methyl-N<sup>4</sup>-hydroxydeoxycytidine showed that deoxyriboside analogs are not necessarily more efficient mutagens than ribonucleosides. No purine pyrimidine deficiency was needed for mutagenesis to occur. (45 refs)

**78-1478 Is Hydrogen Fluoride Mutagenic in Plants?** (Eng) Temple, P. J. (Phytotoxicology Section, Air Resources Branch, Ontario Ministry of the Environment, Toronto, Ontario, M5S 1Z8, Canada); Weinstein, L. H. *J. Pollut Control Assoc* 28(2): 151-152; 1978.

Tomato plants (*Lycopersicon esculentum*) were exposed to 6.7, 1.2 or 0 ppb hydrogen fluoride (HF) and examined for mutagenic effects. No effect on chromosome and no phenotypic abnormalities in the progeny of exposed plants were



However, onion (*Allium cepa*) root tips exposed to 10<sup>-2</sup> HF for 24 hr had chromosomal aberrations and possible mutations. A wide variety of plants will have to be tested to determine the mutagenicity of HF. (13 refs)

**78-1479 Plant-Mediated Activation of Mutagens (Meeting Abstract).** (Eng) Scott, B. R. (Lab. Environmental Mutagenesis, NIEHS, Research Triangle Park, NC, 27709); Sparrow, A. H.; Lamm, S. S.; Schairer, L. A. *Environ Health Perspect* 20: 235; 1977. (no refs)

**78-1480 Absence of Strand Breaks in Deoxyribonucleic Acid Treated with Metronidazole.** (Eng) LaRus, N. F. (Gastroenterology Unit, Mayo Clinic, Rochester, MN 55901); Tomasz, M.; Kaplan, D.; Muller, M. *Antimicrob Agents Chemother* 13(1): 19-24; 1978.

determine whether DNA degradation is involved in the toxic, radiosensitizing, and mutagenic activities of metronidazole (MN) in vivo, this mode of MN-DNA interaction was evaluated by melting curve and viscosity measurements by neutral and alkaline sucrose gradient centrifugation. Three sources of DNA were used, calf thymus DNA and labeled and unlabeled DNA from a wild-type strain of *Staphylococcus pneumoniae* (R36A) and T7 phage DNA. The DNA's were treated with MN alone or MN reduced by sodium dithionite in the presence of DNA, a process that induces covalent binding of MN to DNA. The drug-to-DNA ratio in the reaction mixture (1:3, 1:2, or 1:500) and the ionic composition of the reaction buffer (1.5 mM HCl-150  $\mu$ M trisodium citrate, pH 7.0; 15 mM NaCl-2 mM citric acid, pH 7.4; 17 mM phosphate buffer, pH 7.4) were varied. Reduced unreduced MN had no effect on the melting temperature, intrinsic viscosity, or sedimentation velocity of all three DNA's under all reaction conditions. However, sodium dithionite alone decreased the intrinsic viscosity of pneumococcal DNA by 25% and decreased the sedimentation velocity of pneumococcal and T7 phage DNA in both sucrose gradients. The results suggest that DNA degradation is not significant in the interaction of MN with nucleic acids. (37 refs.)

**78-1481 Effect of Selenium and Other Antioxidants on the Mutagenicity of Malonaldehyde (Meeting Abstract).** (Eng) Shamberger, R. J. (Cleveland Clinic Foundation, Cleveland, OH, 44106); Beaman, K. D.; Corlett, C. Kasten, B. L. *Fed Proc* 37(3): 261; 1978. (no refs)

**78-1482 Dietary Antioxidants Decrease Urinary Mutagenic Metabolites of Benzo(a)pyrene and En-**

**hance Hepatic Glutathione S-Transferase Activities (Meeting Abstract).** (Eng) Benson, A. M. (Johns Hopkins Medical Inst., Baltimore, MD, 21205); Batzinger, R. P.; Bueding, E.; Cha, Y. N.; Talalay, P. *Fed Proc* 37(3): 596; 1978. (no refs)

**78-1483 Tert-butyl-hydroxyanisole and Antimicrobial Agents Decrease Levels of Mutagenic Metabolites (Meeting Abstract).** (Eng) Batzinger, R. P. (Johns Hopkins Medical Inst., Baltimore, MD, 21205); Ou, S. Y.; Bueding, E. *Fed Proc* 37(3): 596; 1978. (no refs)

**78-1484 Effect of 2(3)-Tert-butyl-4-hydroxyanisole (BHA) Administration on Hepatic Epoxide Hydratase and Other Enzymes (Meeting Abstract).** (Eng) Cha, Y. N. (Johns Hopkins Medical Inst., Baltimore, MD, 21205); Martz, F. *Fed Proc* 37(3): 596; 1978. (no refs)

**78-1485 The Drug and Carcinogen Metabolism System of Rat Colon Microsomes.** (Eng) Fang, W. F. (Dept. Biochemistry and Molecular Biology, Univ. Texas Medical Sch., Houston, TX, 77025); Strobel, H. W. *Arch Biochem Biophys* 186(1): 128-138; 1978.

Mucosal microsomes were isolated from male Sprague-Dawley rat colon, and their drug and carcinogen metabolism system was investigated. The microsomal hydroxylation of benzphetamine (BPA), ethylmorphine, p-nitroanisole, and p-nitrophenetole was increased two to four times by pretreating the rats with phenobarbital sodium (75 mg/kg ip) on days 5-3 before sacrifice and hydrocortisone 21-sodium succinate (50 mg/kg ip) on days 2-1 before sacrifice. Colon microsomal benzo(a)pyrene (BP) hydroxylation was inducible 35-fold by pretreatment with  $\beta$ -naphthoflavone (80 mg/kg ip). Phenobarbital/hydrocortisone pretreatment also induced a fourfold increase in the specific content of colon microsomal cytochrome P-450, but  $\beta$ -naphthoflavone pretreatment caused a shift in the reduced CO-difference spectrum peak to 448 nanometers and an eightfold increase in the specific content of this cytochrome. SKF 252-A (2.0 mM) inhibited BPA hydroxylation by 77%. 7,8-Benzoflavone (10  $\mu$ M), however, inhibited BP hydroxylation by colon microsomes by 76% and hydroxylation by liver microsomes by 44%. CO inhibited BPA and BP hydroxylation by colon microsomes 30% and 51%, respectively, at an oxygen:CO ratio of 1:10. The  $K_m$  values of colon microsomal cytochrome P-450 reductase for the artificial electron acceptors cytochrome c, dichloroindophenol, and ferricyanide (10-77  $\mu$ M) were in agreement with those for purified rat liver cytochrome P-450 reductase. These findings indicate that colon microsomes can hydroxylate drugs and polycyclic hydrocarbons by a cytochrome P-450-dependent system similar to that found in liver microsomes. (43 refs)



- 78-1486 Mutation Assay in Diploid Human Lymphoblasts: Methodological Aspects.** (Eng) Thilly, W. G. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); DeLuca, J. G.; Hoppe, H.; Liber, H. L.; Penman, B. W. *J Environ Pathol Toxicol* 1(2): 91-99; 1977.

A quantitative assay for mutation at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus of human lymphoblasts was developed based on the fact that loss of this activity confers resistance to the toxic effects of 6-thioguanine (6TG) at 10  $\mu\text{g/ml}$  in normal medium. A lymphoblast culture in exponential growth is exposed to a known initial concentration of a test chemical. Following treatment, the cells are precipitated by brief centrifugation and resuspended in fresh medium. Cell number is determined, and a culture sample is suspended in agarose-containing medium over a human fibroblast feeding layer. Colonies are counted after 2 wk to determine toxicity. After an additional 2 wk (the growback or phenotypic lag period), induced mutation is determined by counting colonies formed in the presence and absence of 5-10  $\mu\text{g/ml}$  6TG when cells are plated in agarose-containing medium. These colonies cannot be detected until 8-14 generations after treatment. The fraction of the population that is 6TG-resistant is calculated by dividing the plating efficiency in the absence of 6TG by the plating efficiency in the presence of 6TG. (6 refs)

- 78-1487 Detection of Mutagenic Impurities in Carcinogens and Noncarcinogens by High-Pressure Liquid Chromatography and the *Salmonella*/Microsome Test.** (Eng) Donahue, E. V. (Dept. Biochemistry, Univ. California, Berkeley, CA 94720); McCann, J.; Ames, B. N. *Cancer Res* 38(2): 431-438; 1978.

High-pressure liquid chromatography (HPLC) was used in combination with the *Salmonella*/microsome test to detect small amounts of mutagenic impurities in 11 carcinogens and noncarcinogens. The mutagenicity of each of the 11 chemicals was compared before and after purification by HPLC, and in four cases there was a significant change in the mutagenic activity after purification. In the case of 7-hydroxy-2-acetylaminofluorene (7-OH-2-AAF), the purified chemical was virtually nonmutagenic. With bis-2,7-acetylaminofluorene and 7-methylbenz(a)anthracene direct mutagenic activity was lost following purification, but activity was retained in the presence of a rat liver microsomal preparation. The mutagenic potency of 2-aminobiphenyl (2-AB) decreased but did not disappear. The impurity in 7-OH-2-AAF that is responsible for its mutagenicity is probably the potent carcinogen 2-acetylaminofluorene; 4-aminobiphenyl is probably the mutagenic impurity in 2-AB. For industrial chemicals, which often contain fairly large amounts of impurities, the *Salmonella* test could be used in the design of industrial syntheses and as a batch process monitor to minimize the introduction of mutagenic impurities. It has also been found that impurities in saccharin (20 ppm of as yet

unidentified impurities) are mutagenic in the *Salmonella* test. Thus, it is possible that the carcinogenicity of saccharin could be due to a potent carcinogenic impurity. (43 refs.)

- 78-1488 Autoradiographic Differentiation of Carcinogenic and Non-carcinogenic Substances by means of the Thymidine-incorporation Screening System.** (Eng) Amlacher, E. (Pathologisches Institut, Friedrich-Schiller-Universität, Zieglmühlenweg 1, DDR-69 Jena, Germany); Bolck, F. *Exp Pathol (Jena)* 14(5): 288-290; 1978.

A carcinogen screening system based on the autoradiographic analysis of DNA synthesis (as measured by  $^3\text{H}$ -thymidine incorporation) was tested on 17 carcinogens and 7 noncarcinogens. Suckling mice (14 to 18 days old) were treated with the dissolved test substances (ip or by stomach intubation) and then  $^3\text{H}$ -thymidine (3  $\mu\text{Ci/g}$  ip) 24 hr later. The animals were killed 50 min after the thymidine injection, and the nuclei of the tubular epithelium of the kidney were examined by autoradiography. All of the carcinogens had a suppressive effect on DNA synthesis that was not shared by the noncarcinogens. This effect represents damage to the DNA synthesis mechanism at an early stage. The damage persists and the rate of DNA synthesis decreases because various replicating units are damaged. (7 refs)

- 78-1489 In Vivo Sister Chromatid Exchange: A Sensitive Indicator of DNA Damage (Meeting Abstract).** (Eng) Nakanishi, Y. (Gerontology Res. Center, NIA, NIDDK, Baltimore, MD, 21224); Kram, D.; Dein, R. A.; Schnekenberg, E. L. *Fed Proc* 37(3): 364; 1978. (no refs)

- 78-1490 Sister Chromatid Exchange Test in Chinese Hamster Cheek Pouch Mucosa (Meeting Abstract).** (Eng) Shuler, C. F. (Dept. Genetics, Children's Hosp., Boston, MA); Latt, S. A. *J Dent Res* 57(A): 211; 1978. (no refs)

- 78-1491 Relationships Between Mutation and Transformation Frequencies in Mammalian Cells Tested "In Vitro" with Chemical Carcinogens.** (Eng) Paronetto, L. (Dept. Oncology, Univ. Genova, Genoa 16132, Italy); Bignami, G. *Mutat Res* 47(1): 53-74; 1977.

Literature data on the frequencies of mutations and transformations induced by mutagenic-carcinogenic compounds in mammalian cells in vitro were compared quantitatively. Transformation frequency data were obtained from 10 experiments on 34 carcinogenic compounds; mutagenic



obtained from 66 experiments on 26 mutagenic compounds; 7 compounds were assayed for both activities. The difference in frequency between structural mutations and transformations was about  $10^2-10^3$ , and it was significant. Findings indicate an absolute difference between structural alterations in single genes are only a part of the mutagenic process. The other steps in this process may be considered as epigenetic. (64 refs)

**78-1492 Tumor Induction by Carcinogenic Agents in Anuran Amphibian *Rana temporaria*.** (Eng) M. V. V. (Lab. Chemical Carcinogenic Agents, N. N. P. Res. Inst. Onkology, Pesochaya-2, Leningrad, USSR). *Arch Geschwulstforsch* 47(5): 385-395; 1977.

Chemical carcinogens were administered to frogs (*Rana temporaria*) and studied for tumor induction. Dime-rosamine, diethylnitrosamine, and dibutyl nitrosamine were administered in the drinking water (5, 50, and 5 ppm, respectively) induced tumors in 44.2%, 43.6%, and 50% of the animals, respectively. Benzidine and 2-acetylaminofluorene administered sc (45-114 mg and 25.5-58.5 mg, respectively) induced tumors in 46.4% and 41.2% of the animals; po administered 60 mg and 30.5 mg, respectively, resulted in no significant tumor induction. p-Dimethylaminoazobenzene and o-azotoluene administered sc at doses of 37-82 mg and 10-20 mg, respectively, resulted in tumors in 30% and 33.3% of the animals, respectively; po administrations of 41 mg and 20 mg, respectively, resulted in no significant tumor induction. Diethyl-ol propionate (480-4,400  $\mu$ g, sc) induced tumors in 100% of the animals. All tumors developed within 15.6-31.9 months and they were located in the liver (hepatocellular cancer, adenomas) or the hemopoietic system (hemocytoblastomas). Administration of diethylhydrazine (sc and po), urea (sc and po), carbon tetrachloride (sc), and 4-[nitro-(2-thiazolyl)]formamide (sc) did not produce tumors. Findings indicate that there is a common mechanism of carcinogenesis in vertebrates and that these animals would be useful for carcinogenesis testing, possibly of environmental pollutants. (15 refs)

**78-1493 Formation of a Mutagenic Drug Metabolite by Intestinal Microorganisms.** (Eng) Batzinger, R. (Dept. Pathobiology, Johns Hopkins Univ., Baltimore, MD 21205); Bueding, E.; Reddy, B. S.; Weisburger, J. H. *Res* 38(3): 608-612; 1978.

Formation of a mutagenic metabolite from a new schistosomicide, 4-isothiocyano-4'-nitrodiphenylamine, which is of mutagenic activity in vitro either alone or in the presence of activating rat liver enzymes, was investigated. Six species of mammals (mouse, rat, hamster, dog, and cebus and rhesus monkeys) receiving this drug at doses between 75 and

500 mg/kg excreted an as yet unidentified mutagenic metabolite. When the isothiocyanate was given to germfree rats, no mutagenic activity was detected in their urine. A coadministration of a single po dose of erythromycin or erythromycinylamine with 25 times the curative schistosomicidal dose of the isothiocyanate completely prevented the formation of a metabolic mutagen while maintaining antiparasitic activity. The organism(s) producing the mutagenic metabolite did not become resistant to erythromycin after almost continuous exposure for 2 mo. These findings indicate that mutagenic activation of drugs can be brought about by some intestinal microorganisms rather than by the metabolic machinery of the host and that mutagenic and chemotherapeutic activities can be completely dissociated from each other. This suggests a new approach for increasing drug safety. (29 refs)

**78-1494 Teratogenic Effects of Waste Anaesthetic Gases (Letter to Editor).** (Eng) Tomlin, P. J. (Dept. Anaesthetics, Univ. Birmingham, Birmingham, England). *Br Med J* 1(6105): 108-108; 1978.

Among the 135 children of 75 anesthetists in Birmingham, England, 5 female children had defects of the musculoskeletal or nervous system. In four cases, only the father was an anesthetist; in the other case, both parents shared the occupation. The types of abnormalities (ependymoma, hydrocephalus from aqueduct stenosis, and others) and the occupation of the father suggest a teratogenic effect of waste anesthetic gases. (10 refs)

**78-1495 Current View on Endogenous Blastomogenic Agents.** (Rus) Raushenbakh, M. O. (Cancer Res. Center, Moscow, USSR). *Vestn Akad Med Nauk SSSR* (10): 78-80; 1977.

Current data on disturbances in tryptophan metabolism in cancer patients and an experimental trial of the blastomogenic activity of indole and aromatic derivatives of tryptophan are reported. Patients with hemoblastosis have an elevated urinary excretion of n-oxyphenyllactic acid, the tryptophan metabolite that has the highest blastomogenic activity in vitro. (no refs.)

**78-1496 Comparison of Serum Oestrogen Concentrations in Post-menopausal Women Taking Oestrone Sulphate and Oestradiol.** (Eng) Anderson, A. B. (Nuffield Dept. Obstetrics and Gynaecology, John Radcliffe Hosp., Headington, Oxford OX3 9DU, England); Sklovsky, E.; Sayers, L.; Steele, P. A.; Turnbull, A. C. *Br Med J* 1(6106): 140-142; 1978.

Mean serum estradiol-17 $\beta$ , estrone, and estrone sulfate levels



were measured in 17 postmenopausal women up to 6 hr after they were treated with piperazine estrone sulfate (1.5 mg po) or estradiol valerate (2 mg po). Each treatment resulted in similar levels of all three estrogens. Max estradiol concentrations were less than those of estrone, but estrone sulfate concentrations were 30 times higher than those of estrone. The similar effects of both estrogen preparations on serum estrogens do not support the suggestion that the risk of endometrial carcinoma is lower in postmenopausal women taking estradiol valerate. (20 refs)

- 78-1497 The Effects of Cyclical Oestrogen Therapy and Sequential Oestrogen/Progestogen Therapy on the Endometrium of Post-menopausal Women.** (Eng) Whitehead, M. I. (Dept. Obstetrics and Gynaecology, King's Coll. Hosp. Medical Sch., Denmark Hill, London, SE5 8RX, England); McQueen, J.; Beard, R. J.; Minardi, J.; Campbell, S. *Acta Obstet Gynecol Scand [Suppl]* (65): 91-101; 1977.

The effects of estrogen (E) and E/progestogen (P) therapy on the endometrium of 127 postmenopausal patients referred to a menopausal clinic were determined. These patients had uterine curettage performed prior to E therapy and at intervals during treatment with three different natural E regimes. At pretreatment curettage, three patients had endometrial carcinoma, two of whom were being given cyclical E therapy with a synthetic E (chlorotrianisene). Of nine patients with endometrial hyperplasia, two were being given cyclical high-dose natural E therapy. Eighty-one remaining patients (34 did not have menopausal syndrome, and they were discharged) with a normal endometrium then received cyclical natural high- or low-dose E or sequential natural E/P therapy. Eleven of 25 given cyclical high-dose E developed endometrial hyperplasia compared to only 1/8 given low-dose therapy. All four patients on sequential E/P regimens continued to have normal endometria. Pretreatment hyperplasia was associated with elevated urinary total E excretion; cyclical E therapy also resulted in high urinary E levels. Eleven patients with endometrial hyperplasia were treated with sequential E/P; in all 11 there was a reversal from endometrial hyperplasia to a normal endometrium. Two patients with pretreatment endometrial hyperplasia developed adenocarcinoma during high-dose E therapy. Five of the nine pretreatment hyperplasia patients had experienced regular withdrawal bleeding, 17 had withdrawal or breakthrough bleeding and 2 had no vaginal bleeding. Of patients with a normal endometrium who developed hyperplasia, 3 had regular withdrawal bleeding, 8 had withdrawal or breakthrough bleeding, and 4 had no bleeding. Of 15 patients on E/P therapy, 14 had regular withdrawal bleeding and 1 had breakthrough bleeding. (13 refs.)

- 78-1498 A Comparison of the Response of Hepatic Mitochondrial Enzyme Activity of the Rat to Dietary Administration of Sex Steroids and Diethylstilbestrol (Meat-**

**ing Abstract).** (Eng) Allaben, W. T. (Southern Illinois Univ. Carbondale, IL, 62901); Gass, G. H. *Fed Proc* 37(3): 59; 1978. (no refs)

- 78-1499 Endometrioid Carcinoma of the Rectum Arising in Endometriosis: Report of a Case.** (Eng) Lo J. V. (704 Route 202 S., Bridgewater, NJ, 08807); Rubin, J.; Salvati, E. P.; Salazar, G. H. *Dis Colon Rectum* 21(1): 56-60; 1978.

A 53-yr-old woman developed an endometrioid carcinoma of the rectum 15 yr after hysterectomy and bilateral salpingo-oophorectomy for pelvic endometriosis. She had been taking diethylstilbestrol (DES: at least 1 mg/day) since the surgery. It is thought that the endometriosis degenerated into a carcinoma in response to DES treatment. (11 refs)

- 78-1500 A Twenty-Five-Year Follow-up Study of Women Exposed to Diethylstilbestrol During Pregnancy.** (Eng) Bibbo, M. (Dept. Obstetrics and Gynecology, Univ. Chicago, and Illinois Cancer Council, HM No. 4, 5841 S. Maryland Ave., Chicago, IL, 60637); Haenszel, M.; Wied, G. L.; Hubby, M.; Herbst, A. L. *N Engl J Med* 298(14): 763-767; 1978.

A health survey was conducted among 693 mothers who had taken diethylstilbestrol (DES) during pregnancy and who had participated in a study during 1951-1952 to evaluate the drug and a comparable group of 668 women who had not taken DES. There were 32 breast cancers among the exposed and 21 among the unexposed women, but the difference was not statistically significant. In addition, no statistically significant differences were detected between the two groups in the frequency and types of uterine, ovarian, and other reproductive tract abnormalities. The occurrence of breast cancer in both groups was compared with the Connecticut State Cancer Registry data for 1963-1965. Compared with the registry data, a significantly higher incidence of breast cancer occurred in both the exposed and unexposed groups over 50 years of age. The reason for this increase is not known, but efforts linked to the selection of mothers participating in the original clinical study cannot be excluded. The findings weigh against implicating maternal DES as a risk factor in breast cancer at present. Continued surveillance is needed to establish whether the women exposed and those not exposed to DES have divergent postmenopausal breast cancer risks. (19 refs)

- 78-1501 DNA Synthesis and DNA Polymerase Activity in Leydig Cells of Diethylstilbestrol-stimulated Mouse Testes.** (Eng) Spruance, S. L. (Div. Infectious Diseases, Dept. Internal Medicine, Univ. Utah Coll. Medicine, Salt Lake City, UT 84132); Wilcox, B.; Richards, O. C.; F



N.; Huseby, R. A.; Samuels, L. T. *Cancer Res* 38(2): 1010-1014; 1978.

Effects of diethylstilbestrol (DES) on DNA synthesis studied in the interstitial cells of mice that develop Leydig cell tumors after prolonged estrogen administration. DES pellets were implanted into 3-mo-old male mice for 3 days and  $^3\text{H}$ -thymidine injected sc 1 hr before sacrifice. DNA synthesis in cells of DES-treated BALB/c mice of the Huseby sub strain, which have a high incidence of Leydig cell tumors, was 5-11 x that in untreated controls. Cells from DES-treated C3H/Bi mice, which have a low incidence of Leydig cell tumors, showed only a 2- to 3-fold increase. Leydig cell concentrates from treated mice had an increased uptake of thymidine in vitro similar to that in vivo. Increase in DNA synthesis was blocked by hydroxyurea. In BALB/c mice, the rise of DNA synthesis to a peak and subsequent recession were paralleled by a rise and fall in DNA polymerase  $\alpha$  activity. DNA polymerase  $\beta$  did not show this variation. In C3H/Bi mice, neither polymerase showed a significant change. The results suggest that early estrogen-stimulated DNA is probably replicative, is not associated with the expected degree of cell division, and is associated with increased DNA polymerase activity. (22 refs.)

2 Genital Tract Anomalies Associated with In Utero Exposure to Diethylstilbestrol. (Eng) Friedman, R. H. (Dept. Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, 77030); Adam, E. *Isr J Med Sci* 15: 353-362; 1978.

Gross anatomic changes and the vaginal epithelial changes in 687 women exposed in utero to diethylstilbestrol are described along with the findings in 66 of these women who agreed to undergo hysterosalpingography. Of 66 women whose time of in utero exposure to DES was between 1950 and 1960, 33% demonstrated gross anatomic changes of the uterus and 44% had colposcopic evidence of vaginal epithelial changes. These changes occurred in a significantly higher percentage of women exposed in utero before the 20th week of gestation. Among 282 women recruited from a review of medical histories, gross anatomic changes of the cervix were significantly more frequent in those < 19 yr old. Gross uterine abnormalities were noted in 44/66 women studied by hysterosalpingography. These changes consisted primarily of malformations in the size and shape of the uterine cavity. (10 refs.)

3 Genital Tract Abnormalities in Mice Following Gestational Exposure to DES (Meeting Abstract). (Eng) McLachlan, J. A. (Lab. Environmental Toxicology, NIEHS, Research Triangle Park, NC, 27709); Newbold, R.; Lamb, J. C. *Environ Health Perspect* 20: 240; 1977. (no refs)

78-1504 The Possible Role of the Enzyme Peroxidase for the Organotropic Toxicity of Diethylstilbestrol (Meeting Abstract). (Eng) Metzler, M. (Inst. Toxicology, Univ. Wurzburg, Versbacher Landstrasse 9, D-8700 Wurzburg, W. Germany); McLachlan, J. A. *Naunyn-Schmiedeberg's Arch Pharmacol* 302(Suppl): R9; 1978. (no refs)

78-1505 Thyroid Hormone Use in Patients with Breast Cancer. Absence of an Association. (Eng) Wallace, R. B. (Dept. Preventive Medicine and Environmental Health, Univ. Iowa, Iowa City, IA, 52242); Sherman, B. M.; Bean, J. A.; Leeper, J. *JAMA* 239(10): 958-958; 1978.

Information on the use and duration of thyroid hormone therapy was obtained in a case-control study involving 79 patients who had surgery for breast cancer and 79 matched controls in order to determine whether there was an association between the therapy and the cancer. No significant difference in the frequency of prior endocrine-related diagnoses was noted between the breast cancer patients and control subjects. A history of thyroid hormone therapy was obtained in an identical proportion of breast cancer and control subjects (13/79, 16.5%). No differences were found in the age at onset of such therapy or in the duration of use between the two groups. Thus, no association was found between breast cancer and thyroid hormone use. (3 refs)

78-1506 Rauwolfia Preparations and Breast Carcinoma. (Rus) Levshin, V. F. (Dept. Epidemiology of Malignant Tumors, Cancer Res. Center, Moscow, USSR). *Sov Med* (9): 145-147; 1977.

To test the hypothesis that there is an association between rauwolfia (RW) administration and breast carcinoma, the incidence of RW-treated hypertension in breast carcinoma patients and in a control group was compared. Since 34.1% of the patients and 33.8% of the controls had RW-treated hypertension, it was concluded that RW does not increase the incidence of breast cancer. (8 refs.)

78-1507 Rapid Development of Keratoacanthoma and Accelerated Transformation into Squamous Cell Carcinoma of the Skin. A Mutagenic Effect of Polychemotherapy in a Patient with Hodgkin's Disease? (Eng) Poleksic, S. (Lab. Service, Veterans Admin. Center, Hampton, VA 23667); Yeung, K. Y. *Cancer* 41(1): 12-16; 1978.

A 59-yr-old man employed as a spray painter presented on June 12 with exertional and paroxysmal nocturnal dyspnea



and wt loss. Physical findings, laboratory data, and left inguinal lymph node biopsy disclosed Hodgkin's disease (HD) with mixed cellularity. A diagnosis of advanced HD, clinical State IV B, was made. Polychemotherapy with the MOPP regimen was started on June 20. The regimen comprised nitrogen mustard (6 mg/m<sup>2</sup> iv on days 1 and 8), vincristine (1.4 mg/m<sup>2</sup> on days 1 and 8), procarbazine (100 mg/m<sup>2</sup> po on days 1-14), and prednisone (40 mg/m<sup>2</sup> on days 1-14); the cycle was repeated every 28 days. Following one course, the cervical, axillary, and epitrochlear lymphadenopathy disappeared, hepatomegaly and inguinal and femoral lymph node enlargement were diminished markedly, and the eosinophilia decreased from 59% to 2% of the WBC differential count. In early July, however, a 1-cm cutaneous lesion with a small ulceration developed on the dorsum of the nose. Biopsy showed keratoacanthoma. The nasal lesion increased in size rapidly following the second and third courses of chemotherapy, and it was excised completely on September 29. The specimen was found to be a well-differentiated squamous cell carcinoma. The cutaneous lesion had been converted into squamous cell carcinoma in only 10 wk. The immunosuppressive effect of the intensive polychemotherapy may have accelerated the malignant transformation. (18 refs.)

- 78-1508 Acute Leukemia Complicating Treatment of Glioblastoma Multiforme.** (Eng) Vogl, S. E. (Div. Medical Oncology, Albert Einstein Coll. Medicine, Bronx, New York, NY, 10461). *Cancer* 41(1): 333-336; 1978.

A 5-yr-old girl developed acute myelomonocytic leukemia following extensive chemotherapy and radiotherapy for glioblastoma multiforme. The leukemia developed in spite of normal peripheral blood counts and only minor treatment-related myelosuppression. It is believed that the leukemia was induced by the chemotherapy and/or radiotherapy. (25 refs)

- 78-1509 Acute Leukemia Following Chlorambucil Therapy of Advanced Ovarian and Fallopian Tube Carcinoma.** (Eng) Morrison, J. (Dept. Internal Medicine, Hematology-Oncology Branch, Naval Regional Medical Center, San Diego, CA, 92134); Yon, J. L. *Gynecol Oncol* 6(1): 115-120; 1978.

A 47-yr-old woman with Stage III ovarian carcinoma and a 47-yr-old woman with adenocarcinoma of the fallopian tube developed acute leukemia following chlorambucil therapy. The former had received cobalt therapy (3,000 rads to the midplane and 5,000 rads to the pelvis) postoperatively. Five months after surgery, chlorambucil therapy was begun at a dose of 2 mg po/day; 14 mo later, the dose was reduced to 2 mg po qod. Therapy was discontinued 1 mo later because of leukopenia. Leukemia was diagnosed 13 mo later. The latter patient received chlorambucil (16 mg po/day) postopera-

tively for 14 mo, at which time therapy was reduced to 8 mg po daily. Chemotherapy was halted 17 mo later. Leukemia was diagnosed 24 mo after cessation of therapy. In an addendum, the report of a 56-yr-old woman who developed di Guglielmo's syndrome after mephalan treatment for Stage I serous cystadenocarcinoma of the ovaries is presented. Therapy had consisted of 30-46 mg mephalan over a 2-yr period with repeat courses every 3-4 wk. Therapy was discontinued after 14 courses because of persistent pancytopenia. (13 refs)

- 78-1510 Reaction of the Metabolic Product of Cyclophosphamide with Synthetic Polynucleotides.** (Meeting Abstract). (Eng) Mehta, J. R. (Dept. Pharmacology and Experimental Therapeutics, Albany Medical Coll., Albany, NY, 12208); Ludlum, D. B. *Fed Proc* 37(3): 596; 1978 (no refs)

- 78-1511 Mutagenicity of Saccharin in *Drosophila*: Possible Role of Contaminants.** (Eng) Kramer, P. G. (Natl. Inst. Public Health, Bilthoven, Netherlands). *Mutat Res* 56(2): 163-167; 1977.

The mutagenicity of two saccharin samples and of two commonly occurring impurities of saccharin, toluenesulfonamide and p-toluenesulfonamide was determined in the *Drosophila* test for sex-linked recessive lethal mutations. The two saccharin samples had been prepared by the same company (Sherwin-Williams) and by the same process (Maumee), a fact that was not known at the beginning of the experiment. The saccharin (5 or 25 mM) and the impurities (5 mM) were administered to the *Drosophila* by dominal injection (0.2 µl/fly) or by a 3-day feeding. Only the saccharin samples enhanced mutation frequency compared with controls. Although the increase was small and somewhat variable, it was reproducible and consistently restricted to brood A, implicating mature sperm as the sensitive germ cells. This sample was tested over a period of 16 months and there was a tendency for the mutation frequency to increase with time. This might be due to the decomposition of the (unknown) mutagenic component of the sample. The other saccharin sample and the impurities were negative. In spite of their similar origin, the different mutagenic activities of the two saccharin samples can still be explained by genetic differences between lot numbers or by the fact that the mutagenic sample was prepared more recently than the nonmutagenic one. This would fit the supposition that the mutagenic contaminant is a rather unstable compound. (10 refs)

- 78-1512 Metabolic Studies of the Nonnutritive Sweeteners Cyclopentylmethylsulfamate and Cyclopentylmethylsulfonate.** (Eng) Mehta, J. R. (Dept. Pharmacology and Experimental Therapeutics, Albany Medical Coll., Albany, NY, 12208); Ludlum, D. B. *Fed Proc* 37(3): 596; 1978 (no refs)



**Sulfamate: Determination of Metabolites in Rat Urine.** (Eng) Spillane, W. J. (Dept. Chemistry, Univ. Coll., Galway, Ireland); Benson, G. A. *J Pharm Sci* 67(2): 226-228; 1978.

urine metabolites of cyclopentylmethyl sulfamate (I) and cyclopentyl sulfamate (II) were determined following their administration to albino Wistar rats. Compound I was administered po in aqueous soln at a dose of 1,450 mg/kg; compound II was administered over 9 days: 200 mg/20 ml water on the first 5 days, none on days 6 and 7, and resumption of dosing on days 8 and 9. With compound I, the av amounts of the cyclopentylmethylamine and cyclopentylmethanol metabolites were 0.11% and 0.12%, respectively. The av recovery of parent compound was 15.4%. These findings support the idea that the main excretory pathway for sulfamates is via the feces. With compound II, the metabolites cyclopentylamine, cyclopentanone, and cyclopentanol decreased after the first 3 days. The av conversion to the amine, ketone, and alcohol was 0.027%, 0.08%, and 0.026%, respectively. (19 refs)

**513 Hepatocarcinogenicity of Wy-14,643, a Hypolipidemic Peroxisome Proliferator (Meeting Abstract).** (Eng) Reddy, J. K. (Northwestern Univ. Med. Sch., Chicago, IL, 60611); Azarnoff, D. L.; Rao, S. Qureshi, S. A. *Fed Proc* 37(3): 232; 1978. (no refs)

**514 Carcinogens Enhance Survival of UV-Irradiated Simian Virus 40 in Treated Monkey Kidney Cells: Induction of a Recovery Pathway?** (Eng) Saragovska, A. R. (Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305); Hanawalt, P. C. *Proc Natl Acad Sci USA* 75: 346-350; 1978.

Treatment of monkey kidney cells with low doses of carcinogens enhanced the survival of UV-irradiated simian virus 40 (SV40). This was true for compounds with UV-like effects (oxin B1 metabolites, N-acetoxyacetylaminofluorene) and compounds with x-ray-like effects (methyl methanesulfonate, ethyl methanesulfonate). This phenomenon resembles the UV reactivation of viruses in eukaryotic cells. The carcinogen-induced enhancement of UV-irradiated SV40 survival was correlated with the inhibition of host-cell DNA synthesis, suggesting that the inhibition is an inducing agent. Irradiated SV40 survival was also enhanced in cells treated with hydroxyurea or cycloheximide to inhibit host DNA synthesis during the early stage of SV40 infection. It is

hypothesized that carcinogen treatment of host cells induces a new recovery pathway that facilitates the replication of damaged DNA, bypassing the lesions and resulting in the enhanced survival of UV-irradiated SV40. This inducible process might represent the expression in eukaryotic cells of the repair of SOS functions (lysogenic induction, cell filamentation, and mutagenesis) previously demonstrated in UV- or carcinogen-treated bacteria. (41 refs)

**78-1515 A Quantitative Host-mediated Mutational Assay of the Hypoxanthine-Guanine Phosphoribosyl Transferase Locus in Chinese Hamster Ovary Cells (Meeting Abstract).** (Eng) Hsie, A. W. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Machanoff, R.; Couch, D. B.; Holland, J. M. *Mutat Res* 53(1): 94; 1978. (no refs)

**78-1516 Association of Lymphomatoid and Sarcomatoid Granulomatoses with Pancreatic Tumors of the Chinese Hamster (Meeting Abstract).** (Eng) Yerganian, G. (Sidney Farber Cancer Inst., Boston, MA, 02115); Paika, I.; Gagnon, H. *Proc Am Assoc Cancer Res* 19: 226; 1978. (1 ref)

*See also:*

- \*(Rev.): 78-1201, 78-1202, 78-1203, 78-1204, 78-1205, 78-1206, 78-1207, 78-1208, 78-1209, 78-1210, 78-1211, 78-1212, 78-1213, 78-1214, 78-1215, 78-1216, 78-1217, 78-1218, 78-1219, 78-1220, 78-1222, 78-1223, 78-1224, 78-1225, 78-1226, 78-1228, 78-1229, 78-1230, 78-1231, 78-1232, 78-1233, 78-1234, 78-1235, 78-1236, 78-1237, 78-1238, 78-1239, 78-1240, 78-1242, 78-1247, 78-1248, 78-1263, 78-1266.
- \*(Phys.): 78-1535, 78-1536, 78-1537, 78-1543, 78-1550.
- \*(Viral): 78-1569, 78-1571, 78-1580, 78-1590, 78-1597, 78-1599, 78-1602, 78-1606, 78-1611, 78-1634, 78-1646, 78-1650.
- \*(Immun.): 78-1684, 78-1697, 78-1704, 78-1733.
- \*(Path.): 78-1744.
- \*(Epid.-Biom.): 78-1757, 78-1761, 78-1763, 78-1764, 78-1766, 78-1769, 78-1773.



## PHYSICAL CARCINOGENESIS

- 78-1517 Cell Viability Studies on the Exfoliated Colonic Cancer Cell.** (Eng) Rosenberg, I. L. (Univ. Dept. Surgery, St. James's Univ. Hosp., Leeds, England); Russell, C. W.; Giles, G. R. *Br J Surg* 65(3): 188-190; 1978.

The hypothesis that colonic cancer cells, desquamated from the tumor and lying free in the lumen of the bowel, are implanted into the bowel wall by the suture needle was tested. Suspensions of desquamated colonic cancer cells were obtained from patients with cancer of the large bowel by colonic exfoliative cytology and from resected specimens of colonic cancer by an ex vivo exfoliation technique. Furthermore, a tumor suspension was obtained from the resected specimens. Although 23/25 tumor homogenate cell suspensions excluded trypan blue (ie, they were alive), none of the exfoliated cancer cell suspensions had viable cells. This finding suggests that suture line recurrence following large bowel cancer surgery is not due to the implantation of desquamated cells by the suture needle. (18 refs)

- 78-1518 Survival of Mice Irradiated with X-Rays at Different Ages.** (Pol) Gajewski, A. K. (Zaklad Ochrony Radiologicznej i Radiobiologii, PZH, ul. Chocimska 24, 00-791 Warsaw, Poland); Chomiczewski, K.; Slowikowska, M. G.; Majle, T. *Rocz Panstw Zakl Hig* 28(6): 615-622; 1977.

The effect of a single dose of x-ray irradiation (300 R) given at different ages (1 day, 1-105 wk) on life-span and causes of death was studied in 789 male inbred mice, and the data obtained were compared with those for 52 nonirradiated controls. Irradiation shortened the life-span only when it was administered on day 1 or during the first 5 wk. Leukemia was the cause of death in 7/40 mice irradiated between weeks 1 and 6, in 6/32 mice irradiated between weeks 7 and 52, and in 1/11 mice irradiated between weeks 78 and 105. Pulmonary adenoma was the cause of death in 17/40 mice irradiated between weeks 1 and 6, in 17/32 mice irradiated between weeks 7 and 52, and in 7/11 mice irradiated between weeks 78 and 105. Death was due to other tumors in one animal irradiated between weeks 1 and 6 and in 7/32 mice irradiated between weeks 7 and 52. The findings indicate that leukemia was the prevalent cause of death in animals irradiated before the 52nd week of life, but irradiation at later dates caused mainly pulmonary adenoma. (12 refs)

- 78-1519 X-Ray Dose Fractionation and Oncogenic Transformations in Cultured Mouse Embryo Cells.** (Eng) Miller, R. (Radiological Res. Lab., Coll. Physi-

cans and Surgeons, Columbia Univ., New York, NY, 10032 Hall, E. J. *Nature* 272(5648): 58-60; 1978.

The effect of x-ray-dose fractionation on the transformation rate of C3H 10T(1/2) clone 8 mouse embryo cells was investigated over the dose range 30-800 rads. The dose rate to cells was in the range 88-102 rads/min. Types II and III foci were scored as transformants. The effect of a single dose was compared with that of the same dose divided into two equal fractions given 5 hr apart. The dose-response curves for induction of transformations by single and split doses crossed at 150 rads. Below this dose level, split doses produced more transformations than a single exposure, but above this level split doses were less effective than a single exposure. The incidence for a fractionated treatment was double that for a single exposure, implying that the two dose fractions, separated by 5 hr, are independent and that there is no interaction between them. This demonstration of an increased incidence of transformation when low x-ray doses are divided must be considered in setting radiation protection levels or in assessing the risk to the public from multiple low-dose-radiation exposures, such as those involved in the medical uses of x-rays. (11 refs)

- 78-1520 Competing-Risk Analysis of Leukemia and Nonleukemia Mortality in X-irradiated, Mice.** (Eng) Robinson, C. V. (Sch. Basic Health Sciences, Health Sciences Center, State Univ. New York at Stony Brook, Stony Brook, NY, 11594); Upton, A. C. *J Natl Cancer Inst* 60(5): 995-1007; 1978.

The theory of competing risks was applied to an analysis of mortality data for acutely x-irradiated male RF/Un mice, in which the cause of death was myeloid leukemia (M), thymic lymphoma (T), lymphosarcoma and reticulum cell sarcoma (L), or other (R). Doses of 0-450 rads were delivered to mice at (A) 5-6 wk of age or (B) 9-10 wk of age to give 11 treatment groups totaling 2,073 mice. For each given cause and group, two estimators were used that measured, respectively, the relative lateness of the corrected time course and the relative corrected incidence. For causes M and T, these were the mean age of the force of mortality distribution (MAF) and the final cumulative force of mortality (cumFM). For causes L and R, the estimators were the adjusted mean age at death (adjMAD) and the cumFM at a cutoff time of 640 days. For causes M and T, the MAF values showed highly significant decreases of the latent periods with dose, through 300 rads. The final cumFM data showed a marked increase of corrected incidence with dose, for both M and T. In addition, data for cause M were consistent with a three-parameter leukemogenic cell model that incorporated two opposing radiation effects: leukemogenic cell potentiation and cell



For cause R, the adjMAD, 100% data showed a general increase with dose and considerable scatter. For cause L, the D, 50% values showed: for Group A mice, a gradual increase with dose through 300 rads; for Group B mice, a significant drop for 150 rads with little change for higher doses. The cumFM, 640-day values for both L and R showed a general increase of corrected incidence with dose. Mortality curves for all causes combined showed the expected life shortening in the 0- to 300-rad range. Furthermore, the standard deviations of the mortality curves were significantly less for animals irradiated at the higher age with the doses, 150, 300, and 450 rads. (16 refs)

**1 The Effect of Normal Ovarian Tissue on the Ovarian Tumorigenesis in X-irradiated Mice.** Komuro, M. (Dept. Anatomy, Teikyo Univ. School of Medicine, Kaga 2-11-1, Itabashiku, 173, Japan). *J Radiat Res* 18(4): 317-321; 1977.

Effect of normal ovarian tissue on ovarian tumorigenesis was investigated in ddY/F and C3H/Tw mice after they were irradiated with 130 R of x-rays at 2 wk of age. ddY/F mice developed primarily luteomas, C3H/Tw mice tubular adenomas. However, when one of the ovaries was shielded during irradiation, no tumors developed. The irradiated ovary was composed of atretic interstitial tissue and granulosa cells, but the shielded ovary had a normal appearance. When the shielded ovary was removed up to 6 mo after irradiation, the incidence of tubular adenomas increased and luteomas decreased. When normal ddY/F and C3H/Tw ovaries were transplanted sc to irradiated recipients, no tumors were noted in the grafts up to 15 mo after transplantation. In contrast, tumors occurred in irradiated ovaries transplanted to nonirradiated hosts at 0.5 or 3 mo after irradiation in ddY/F mice and at 0.5 mo in C3H/Tw mice. The tumors in the former were exclusively luteomas, those in the latter were exclusively tubular adenomas. Thus, hormonal conditions in the early stages of tumorigenesis may determine the type of ovarian tumor. With these mice, however, genetic factors may also play a role in the type of tumor that develops. (0 refs)

**2 Does Fetal Irradiation Cause Childhood Malignancies? (Meeting Abstract).** (Eng) Burch, P. R. (Medical Physics, Leeds Univ., Leeds, England). *Br J Radiat Oncol* 1(602): 146; 1978. (no refs)

**Gastric Carcinoma 16 Years After Gastric Lymphoma Irradiation.** (Eng) Ettinger, D. S. (Oncology Center, Room 130, Johns Hopkins, Baltimore, MD). *Am J Gastroenterol* 68(5): 485-488; 1977.

A 71-yr-old man developed an infiltrating signet-ring type of mucus-secreting adenocarcinoma of the stomach 16 yr after palliative resection and radiation therapy of a gastric lymphoma. The patient had received a minimum midplane dose of 2,000 rads and a max tumor dose of 2,600 rads at a daily dose of 200 rads for 5 mo. Although the cancer could have developed as a result of changes secondary to surgery, the possible association with radiation therapy cannot be denied. (8 refs)

**78-1524 Derivation and Characterization of Established Primary Radiation-induced Thymoma Cultured from C57BL/6 Mice (Meeting Abstract).** (Eng) Lee, J. C. (Basic Res. Program, NCI-Frederick Cancer Res. Center, Frederick, MD, 21501); Bucana, C. *Proc Am Assoc Cancer Res* 19: 93; 1978. (no refs)

**78-1525 Neoplasia in Grafts of Known Numbers of Irradiated or Unirradiated Rat Thyroid Cells (Meeting Abstract).** (Eng) Clifton, K. H. (Human Oncology Dept., Wisconsin Clinical Cancer Center, Univ. Wisconsin Medical Sch., Madison, WI, 53706); DeMott, R. K.; Mulcahy, R. T.; Gould, M. N. *Proc Am Assoc Cancer Res* 19: 227; 1978. (no refs)

**78-1526 Incidence, Prevalence and Characteristics of Radiation-induced Thyroid Tumors.** (Eng) Schneider, A. B. (Dept. Medicine, Michael Reese Hosp., 29th St. and Ellis Ave., Chicago, IL, 60616); Favus, M. J.; Stachura, M. E.; Arnold, J.; Arnold, M. J.; Frohman, L. A. *Am J Med* 64(2): 243-252; 1978.

Of 5,266 patients known to have received radiation treatments of the head and neck area, 2,578 were contacted and 2,189 responded in an effort to detect radiation-induced thyroid cancers. A majority of the patients had received conventional x-irradiation to the tonsil-nasopharyngeal region. Of the responding patients, 713 had nodular disease at some time. A total of 209 patients had had thyroid surgery before 1974 (beginning of this study and prior to mass media publicity), 66 of whom had carcinoma, 112 benign disease. After 1974, 337 patients underwent an initial surgery, with 115 having thyroid carcinomas and 202 benign disease. No risk factors were found to distinguish between malignant and benign disease. Of 50 patients who were examined and who had a history of prior thyroid surgery, 18 had evidence of new tumors. In this group, thyroid suppressive therapy appeared to prevent recurrences. The number of patients undergoing thyroid surgery for the 10 yr immediately following radiation treatment was low; it then increased for the next 25 yr before declining. However, further studies are necessary before it



can be concluded that the risk decreases after 25 yr. It is suggested that any patient who has undergone thyroid surgery for a radiation-induced nodule be given thyroid suppression therapy to lessen the chances of recurrence. (17 refs)

**78-1527 Coexistent Parathyroid Adenomas and Thyroid Carcinoma. Can Radiation Be Blamed? (Eng)**

LiVolsi, V. A. (Dept. Pathology, Yale Univ. Sch. Medicine, 310 Cedar St., New Haven, CT, 06510); LoGerfo, P.; Feind, C. R. *Arch Surg* 113(3): 285-286; 1978.

The history of 38 patients with both parathyroid adenomas and nonmedullary thyroid carcinoma was reviewed to test the hypothesis that ionizing radiation may be a cause of the neoplasia. Specific data concerning radiation exposure were obtained in 32/38 patients, and only 1 of these had a history of face and neck irradiation for acne 20 yr earlier. These results indicate that the association of parathyroid adenomas and thyroid carcinoma cannot be explained on the basis of prior neck radiation. (29 refs)

**78-1528 Fibrosarcoma in Previously Irradiated Skin.**

(Jpn) Hori, M. (Dept. Dermatology, Nagasaki Chuo Natl. Hosp., Ohmura-shi, Nagasaki Prefecture 856, Japan); Saeki, T.; Satomi, G.; Egami, K. *Nishinippon Hinyokika* 39(6): 880-885; 1977.

A 45-yr-old woman developed a radiation-induced fibrosarcoma on the buttock and died within 2 yr of metastases to the lung and subclavicular lymph nodes. Both light and electron microscope studies confirmed the diagnosis of fibrosarcoma. The importance of differentiating a fibrosarcoma from other fibrous tumors, such as dermatofibrosarcoma protuberans, granuloma pyogenicum, and fibrous histiocytoma, is emphasized. (7 refs)

**78-1529 Radiation-Associated Chronic Myelogenous Leukemia (CML) In Younger Individuals**

(Meeting Abstract). (Eng) Shimaoka, K. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Sokal, J. E. *Proc Am Assoc Cancer Res* 19: 327; 1978. (no refs)

**78-1530 Dose-Response Relationship in Radiogenic Breast Cancer (Letter to Editor). (Eng)**

Bross, I. D. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Shore, R. E.; Land, C. E.; McGregor, D. H.; Boice, J. D. *J Natl Cancer Inst* 60(4): 727-730; 1978.

In a criticism of a previous article, it is maintained that the dose-response curve for radiogenic breast cancer does not follow a linear function. The curve would be expected to reflect the balancing of factors involved in carcinogenesis, and this would vary among different dose ranges. At background doses, the curve would reflect a balance between genetic damage and repair; at high doses, the balance would be between genetic damage and cell kill. Use of this linear relationship to extrapolate risk to low doses would not provide protection to the public. In three rebuttals, it is indicated that the response does reflect a linear relationship. The low-dose studies indicate the approx linear function up to a high dose level above which cell killing or related high-dose phenomena diminish the response. (18 refs)

**78-1531 Estimation of Breast Doses and Breast Cancer Risk Associated with Repeated Fluoroscopic**

**Chest Examinations of Women with Tuberculosis. (Eng)** Boice, J. D. (Environmental Epidemiology Branch, NIH, Room 3C07, Landow Building, Bethesda, MD, 2001); Rosenstein, M.; Trout, E. D. *Radiat Res* 73(2): 373-378; 1978.

A follow-up study was conducted of 1,047 female pulmonary tuberculosis patients who received repeated fluoroscopic examinations of the chest between 1930 and 1954. Medical record abstraction, physician interview, patient contact, machine exposure measurements, and absorbed dose calculations were combined to estimate average breast radiation doses. Breast cancer risk was estimated by a methodology that considers breast size and composition, patient orientation, x-ray field size and location, beam quality, type of examination, machine exposure rate, and exposure time during fluoroscopic examinations. The best estimate for the risk of radiation-induced cancer for the women living longer than 10 yr after the initial fluoroscopic exposure is 6.2 excess breast cancers per million woman-year-rad. When breast cancer risk is considered as a function of absorbed dose in the breast, there is a linear dose-response relationship over the range of estimated doses. Multiple low-dose exposures may be expected to produce fewer deleterious effects than a single exposure of the same total dose; however, the fact that this does not suggest that the radiation damage is cumulative. When assessing the possible radiation risk associated with mammography, it should be assumed that the risk is present at the low dose levels involved and that the total risk will be proportional to the total radiation dose received during the lifetimes of exposed women. (16 refs)

**78-1532 Geomagnetism, Cancer, Weather and Cosmic Radiation. (Eng)**

Archer, V. E. (Public Health Service, United States Dept. Health, Education and Welfare, Room 433, 350 S. Main, Salt Lake City, UT, 84101). *Health Phys* 34(3): 237-247; 1978.



association between cancer incidence and various geographic and meteorological phenomena was investigated. The isometric cancer death rates and the depth contours of the last ice age glacier in North America corresponded to the isometric horizontal geomagnetic intensity lines. This association held for cancer of the kidney, breast, female reproductive organs (except cervix), stomach, testis, prostate, connective tissue, colon, rectum, thyroid, brain, and nervous system for multiple myeloma, lymphoma, leukemia, and Hodgkin's disease. Nonconforming sites included the respiratory system, salivary glands, uterine cervix, pancreas, biliary passages, liver, urinary bladder, eye, mouth, larynx, nasopharynx, and endocrine glands other than the thyroid. When geomagnetic flux was held constant, an association with latitude was demonstrated. Similar associations between cancer incidence and horizontal geomagnetic flux were demonstrated on a worldwide basis. Nonuniform stratospheric heating resulting from the influence of the earth's geomagnetic field on cosmic and solar radiation may influence the weather conditions on the earth and, correspondingly, the cancer incidence. (73 refs)

533 **Effect of Ozone Variation on Disease in Great Britain: I. Skin Cancer.** (Eng) Leach, J. F. (Environmental Sciences Group, Commercial Aircraft Div., British Aircraft Corp., Filton, Bristol, England); Beadle, P. R.; Kingstone, A. R. *Aviat Space Environ Med* 49(3): 512-516; 1978.

Ozone levels in the Oxford area of Great Britain between 1952 and 1972 were compared with the skin cancer records for that same period. There was a 10% increase in the ozone level during this period; this would account for a reduction in the annual radiation dose of 16.4% at the skin surface, 10% below the stratum corneum, and 15.6% below the basal epidermis. Between 1952 and 1962, there was a decrease in the incidence of both basal and squamous cell carcinoma in Bristol; the carcinoma data for Oxford were not complete, but they indicated a fall in squamous cell carcinoma. Melanoma figures for both cities, however, showed an unexplainable rise during this period. At the start of the second decade, skin carcinoma incidence in Bristol and Oxford showed a sudden upsurge. It is concluded that carcinomas of the skin do respond to changes in UV radiation, ozone levels, and that incidence is a function of cumulative exposure. Changes during the second decade could have been related to a reduction in particulate material in the air due to the Clean Air Acts. The reason for the melanoma increase is unknown. (8 refs)

534 **Effect of Heat, Wind, and Humidity on Ultraviolet Injury.** (Eng) Owens, D. W. (Sect. Dermatology, Kelsey-Seybold Clinic, Houston, TX, 77030). *Int J Dermatol* 17(1): 52-54; 1978.

Acute and chronic studies were performed with mice to determine the effects of heat, wind, and humidity on UV-induced skin injury. Increases in all three environmental factors enhanced UV injury and carcinogenesis, but the reason for this enhancement is not known. (8 refs)

78-1535 **Excision Repair Following Ultraviolet Irradiation in Toluene-treated *Escherichia coli*.** (Eng) Dorson, J. W. (Marrs McLean Dept. Biochemistry, Baylor Coll. Medicine, Houston, TX, 77030); Moses, R. E. *Tex J Science* 28(1-4): 7-18; 1977.

Excision repair was studied in cells treated with toluene and exposed immediately afterward to 6 joules/m<sup>2</sup>/min UV radiation. After irradiation, wild-type cells incubated in complete reaction mixtures containing the appropriate substrates for DNA synthesis, including ATP, demonstrated little breakdown in the DNA. Excision repair was studied using agents that blocked the individual repair processes. Two pathways involving DNA polymerase I were observed. In the first, irradiated cells were allowed to accumulate incisions in the absence of repair synthesis and then repair synthesis was allowed. In wild-type cells, this resulted in a rapid reformation of high-mol-wt DNA. The other approach involved direct stimulation of the polymerase by adding nicotinamide mononucleotide, which blocks polynucleotide ligase activity. This resulted in a large increase in the amount of repair synthesis following UV that was specific for DNA polymerase I. It is concluded that the repair synthesis catalyzed by DNA polymerase I is an efficient process, repair synthesis is easily terminated by polynucleotide ligase, and that few nucleotides are inserted into the damage site. (12 refs)

78-1536 **Biological Relevance in Diploid Human Cells of Excision Repair of Lesions in DNA Caused by Ultraviolet Light or N-AcO-AAF (Meeting Abstract).** (Eng) Maher, V. M. (Michigan State Univ., East Lansing, MI, 48824); Dorney, D. J.; Konze-Thomas, B.; Mendrala, A.; McCormick, J. J. *Proc Am Assoc Cancer Res* 19: 70; 1978. (no refs)

78-1537 **Correlation Among Neoplastic Transformation, Somatic Mutation and Direct DNA Perturbation (Meeting Abstract).** (Eng) Tsutsui, T. (Div. Biophysics, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205); Ts'o, P. O. *Proc Am Assoc Cancer Res* 19: 89; 1978. (no refs)

78-1538 **Evidence That Pyrimidine Dimers in DNA Can Give Rise to Tumors.** (Eng) Hart, R. W. (Dept.



Radiology, Ohio State Univ., Columbus, OH 43210); Setlow, R. B.; Woodhead, A. D. *Proc Natl Acad Sci USA* 74(12): 5574-5578; 1977.

The Amazon molly, *Peocilia formosa*, was used to investigate UV radiation-induced tumors. Because the fish grows in clones, cells from one animal may be transplanted to another without danger of rejection. Thyroid cells and adjacent tissue were irradiated with UV light in vitro and injected into the abdominal cavity of isogenic recipients. In all experiments, exuberant thyroid growth was seen in all fish receiving a single injection of  $4 \times 10^5$  cells that had been exposed to an av of 10-20 joules/m<sup>2</sup> UV radiation. If the radiation was followed, but not preceded, by photoreactivating illumination, the yield of thyroid growth was markedly decreased. Other investigations have shown that photoreactivation monomerizes UV-induced cyclobutylpyrimidine dimers in DNA but does not affect other photoproducts. These observations argue strongly that the initial lesions resulting in tumor formation are pyrimidine dimers in DNA. (21 refs.)

**78-1539 Properties of Ultraviolet Light-induced Suppressor Lymphocytes Within a Syngeneic Tumor System.** (Eng) Spellman, C. W. (Dept. Pathology, Univ. Utah Medical Center, Salt Lake City, UT, 84132); Daynes, R. A. *Cell Immunol* 36(2): 383-387; 1978.

The properties of UV-induced suppressor lymphocytes in female C3Hf/HeN mice were investigated. In mice given 8 wk of UV treatment ( $1.79 \times 10^3$  ergs/cm<sup>2</sup>/sec for 30 min/day, 5 times/wk), the suppressor cells were nylon-nonadherent cells. Normal mice could be made susceptible to supporting the progressive growth of a transplanted syngeneic UV tumor (RD87) by the adoptive transfer of whole, nylon-nonadherent, or nylon-nonadherent plus nylon-adherent spleen cells from 8-wk-treated mice. A dose of about  $2 \times 10^7$  nonadherent cells was needed to suppress the anti-UV tumor response. The data also indicated that nylon wool fractionation of UV spleen cells also enriches for suppressor cell activity. Spleen cells from 8- and 5-wk-treated mice were then transferred to normal mice to determine whether the suppression was a long-lived phenomenon. The results indicated that although UV-irradiated mice were susceptible to supporting the growth of transplanted syngeneic UV tumors long after termination of the UV exposures, adoptively transferred suppression waned and normal mice exhibited time-dependent recovery. (21 refs)

**78-1540 Isolation of DNA Repair Mutants of Chinese Hamster Cells (Meeting Abstract).** (Eng) Schultz, R. (Dept. Human Development, Michigan State Univ., E. Lansing, MI, 48824); Chang, C. C.; Trosko, J. E. *Proc Am Assoc Cancer Res* 19: 28; 1978. (no refs)

**78-1541 Molecular Mechanisms of DNA Repair Defects and Heterogeneity in Xeroderma Pigmentosum.** (Jpn) Takebe, H. (Radiation Biology Center, Kyoto Univ., Kyoto, Japan). *Jpn J Hum Genet* 22(2/3): 129-136; 1977.

The clinical characteristics and DNA repair capacity of 50 Japanese patients with xeroderma pigmentosum (XP) were determined. More than 50% of the patients were children < 13 yr of age. Genetic complementation tests, performed on 23 cell strains, indicated that 21 belonged to Group A, 1 to Group D, and 1 to Group E. Group C, the most frequent type in Europe and the US, was not represented. Host-cell reactivation of UV-irradiated herpes simplex virus was the most reliable method for the diagnosis of XP, and it reflected the relative capacity of excision repair. The high frequency of XP patients with low DNA repair capacities, including Group A patients, may account for the apparent high frequency of XP patients in Japan. The age distribution of the cancer-bearing patients and their DNA repair characteristics suggest that almost all XP patients, except those with nearly normal levels of excision repair, have or will develop skin cancers. (13 refs)

**78-1542 Correlation of Cellular and Molecular Repair Process in Xeroderma Pigmentosa (XP) and Ataxia Telangiectasia (AT) Fibroblasts: A Possible Explanation for the High Tumor Incidence in These Patients (Meeting Abstract).** (Eng) Weichselbaum, R. R. (Joint Center Radiation Therapy, Harvard Medical Sch., 50 Binney St. Boston, MA, 02115); Little, J. B. *Proc Am Assoc Cancer Res* 19: 19; 1978. (no refs)

**78-1543 An Evaluation of Tween 80 Effects on the Survival and DNA Repair in *Escherichia coli* Following UV or Gamma Irradiation.** (Eng) Chi, R. K. (Dept. Biochemistry, Johns Hopkins Univ., Sch. Hygiene and Public Health, Baltimore, MD, 21205); Scoocca, J. J.; Huang, P. C. *Mutat Res* 49(1): 1-8; 1978.

The effects of Tween 80 (polyoxyethylene sorbitan monosorbate) on the repair of radiation-induced DNA lesions were investigated in *Escherichia coli* K12-SH28. The bacteria adapted well to medium containing Tween 80 at concentrations up to 10%. There was no significant difference in the viability of cells incubated with or without Tween 80. When growth was monitored by turbidity measurements, however, a significant effect was noted in the presence of Tween 80. For a given cell density, the A<sub>650</sub> reading for cultures without and with 5% or 10% Tween 80 was 0.80, 0.48, and 0.36 respectively. After irradiation of *E. coli* with 6.5 joules/m<sup>2</sup> or 6/5 joules/cm<sup>2</sup>, the presence of up to 1% Tween 80 in the repair incubation mixture did not affect the removal of thymine dimers. Similar results were obtained following exposure of bacteria to gamma irradiation. These findings do not



contradict the suggestion that Tween 80 is cocarcinogenic in eukaryotes; it may be synergistic when the entry of carcinogenic compounds into cells requires enhancement. (18 refs)

78-1544 **A New Transplantable Radiation Induced Leukemia (RIL) in Strain 2 Guinea Pigs (Meeting Abstract).** (Eng) Saijo, N. (Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Murphy, S.; Peters, L.; Grdina, D. *Proc Am Assoc Cancer Res* 19: 156; 1978. (no refs)

78-1545 **Chemiluminescence of Plasma  $\alpha$ - and  $\beta$ -Lipoproteins of Rats Irradiated with Fast Neutrons.** (Rus) Serkiz, Ya. I. (Inst. Problems in Oncology, Acad. Sci. Ukrainian SSR, Kiev, USSR); Kovtun, T. V.; Ryabova, E. Z.; Chebotarev, E. E. *Radiobiologiya* 17(6): 803-806; 1977.

The effect of ionizing radiation on the ultraweak luminescence kinetics of plasma lipoproteins was studied in albino random-bred rats. The animals were irradiated at age 3 wk with 100 rads of fast neutrons. They were sacrificed 3, 6, 9, and 12 mo later, and the  $H_2O_2$ -induced chemiluminescence of plasma  $\alpha$ - and  $\beta$ -lipoproteins was assessed. Three months after irradiation, rats showed a significant increase in total luminescence (101.2 units, compared to 62.1 units in controls). One year after irradiation, when rats had developed radiation-induced malignant tumors of the mammary gland, the luminescence parameters showed further changes: decrease of the first peak of  $\alpha$ -lipoprotein luminescence and increase in the intensity of the second peak, along with an increase in the first peak of  $\beta$ -lipoprotein luminescence and complete disappearance of the second peak. (20 refs.)

78-1546 **Transformation of Mammalian Cells In Vitro by Low Doses of Monoenergetic Neutrons and Carbon Ions (Meeting Abstract).** (Eng) Borek, C. (Radiobiology Res. Lab., Coll. Physicians and Surgeons, 630 W. 168th St., New York, NY, 10032); Hall, E. J. *Proc Am Assoc Cancer Res* 19: 39; 1978. (no refs)

78-1547 **Suppressor Cell Activity in Spleen Cell Cultures from  $^{89}Sr$  Treated Mice (Meeting Abstract).** (Eng) Levy, E. M. (Boston Univ. Sch. Medicine, Boston, MA, 02118); Merluzzi, V. J.; Kumar, V.; Bennett, M.; Coopland, S. R. *Proc Am Assoc Cancer Res* 19: 77; 1978. (no refs)

78-1548 **Deposition, Retention and Excretion of Industrial Mixed Oxide Aerosols Using the Laboratory Rat (Meeting Abstract).** (Eng) Stanley, J. A. (Inhalation Toxicology Res. Inst., P. O. Box 5890, Albuquerque, NM, 87115); Mewhinney, J. A.; Eidson, A. F.; Mo, T. *Health Phys* 33(6): 666-667; 1977. (no refs)

78-1549 **The Retention of Plutonium in Hepatocytes and Sinusoidal Lining Cells Isolated from Rat Liver.** (Eng) Grube, B. J. (Radiobiology Div., Dept. Anatomy, Univ. Utah, Salt Lake City, UT, 84132); Stevens, W.; Atherton, D. R. *Radiat Res* 73(1): 168-179; 1978.

The distribution of plutonium in the extravascular and cellular compartments of rat liver was studied following the iv injection of  $^{239}Pu(IV)$  citrate (0.9 Ci/kg). The quantity of Pu in the whole liver reached a max 2 days after injection and then declined. Significant quantities of both protein and Pu were found in the perfusate of livers perfused with modified Hanks buffer. The amounts of Pu in isolated and purified hepatocytes and sinusoidal lining cells were determined following collagenase digestion of the buffer-perfused liver. The retention of  $^{239}Pu$  by the two cell populations and the whole liver declined. However, Pu was lost from hepatocytes more rapidly than it was from sinusoidal lining cells, so that by 1 day after injection the amount of Pu/mg of protein in sinusoidal cells was greater than that in hepatocytes. The association of Pu with cells of both populations was verified by autoradiography. Fractionation of hepatocytes into subcellular components indicated that the amount of Pu in each fraction decreased at the same rate as the amount in the whole liver. The absence of liver tumors in rats following Pu administration is due to its rapid loss from the liver; rats succumb to the skeletal effects of Pu when given at doses that induce bile duct tumors in dogs, which lose Pu from the liver at a much slower rate than rats. (25 refs)

78-1550 **Mutagenicity of Fume Particles from Metal Arc Welding on Stainless Steel in the Salmonella/Microsome Test.** (Eng) Maxild, J.; Andersen, M.; Kiel, P. (Dept. Microbiology, Royal Danish Sch. Pharmacy, 2 Universitetsparken, 2100 Copenhagen O, Denmark); Stern, R. M. *Mutat Res* 56(3): 235-243; 1978.

The mutagenic activity of fume particles from metal arc welding on stainless steel (ss) was investigated by the *Salmonella typhimurium* system with strains TA100 and TA98. In both strains, the background lawns on the plates without S-9 mix were inhibited by fume particles from ss welding at a concentration  $>0.4$ - $0.5$  mg/plate for manual metal arc (MMA)/ss welding and  $>2.0$ - $3.0$  mg/plate for metal inert gas (MIG) welding. At concentrations  $>1.75$  mg MMA welding fume particles/plate, the growth of the background lawn in plates



with S-9 mix was inhibited. With TA100, the number of revertant colonies increased with increasing concentration of particles from MMA/ss welding, both with and without the S-9 mix. However, the increase in the number of revertant colonies observed with fume particles from MIG/ss welding nearly disappeared with S-9. Fume particles produced by welding on mild steel (ms) did not increase the number of revertant colonies with increasing concentration. Revertant colonies induced by MMA/ss and MIG/ss welding fume particles in TA98 increased with increasing concentration both with and without the S-9 mix. There was no increase in the number of revertants with increasing concentrations of fume particles produced by MIG/ms or MMA/ms. MMA/ss produced particles of higher mutagenic activity than MIG/ss welding, and particles produced by MIG under short-arc transfer conditions were more mutagenic than those produced by spray-arc transfer. (12 refs)

**78-1551 Tin Needles at the Intrascrotal Site in Mice (Meeting Abstract).** (Eng) Bischoff, F. (Cottage Hosp. Res. Inst., Santa Barbara, CA, 93105); Bryson, G. *Proc Am Assoc Cancer Res* 19: 9; 1978. (4 refs)

**78-1552 Ability of Hamster Trachea Cultures to Distinguish Particulate Carcinogens (Meeting Abstract).** (Eng) Frank, A. L. (Environmental Sciences Lab.,

Mount Sinai Sch. Medicine, New York, NY, 10029). *Proc Am Assoc Cancer Res* 19: 97; 1978. (no refs)

**78-1553 Notes on Two Cases of Thorotrastosis.** (Ita) Ippoliti, G. (Istituto di Clinica Medica Generale e Terapia Medica A. Ferrata, Pavia, Italy); Casirola, G.; Marini, G.; Barosi, G. *Minerva Med* 68(59): 3981-3988; 1977

Thorium dioxide particles were found in the bone marrow, liver, and spleen of a 74-yr-old man 35 yr after thorotrast arteriography. Erythroblastic bone marrow hyperplasia was also seen. Thorotrast particles were found in the femoral vessels of another patient 34 yr after thorotrast angiography of the leg. Both cases were detected serendipitously. (40 refs)

*See also:*

\*(Rev.): 78-1242, 78-1243, 78-1244, 78-1245, 78-1246, 78-1247, 78-1263, 78-1264, 78-1270.

\*(Chem.): 78-1309, 78-1414, 78-1508, 78-1514.

\*(Viral): 78-1611, 78-1650.

\*(Path.): 78-1744.

\*(Epid.-Biom.): 78-1756, 78-1770, 78-1772, 78-1773



## VIRAL CARCINOGENESIS

8-1554 **Inter-relationship Between Genes Controlling Endogenous Virus Expression and Those Controlling Susceptibility to Exogenous RNA Tumour Viruses: Evidence for Linkage Between the Group Specific Antigen and Tumour Virus *e* Loci.** (Eng) Pani, P. K. (Houghton Poultry Res. Station, Houghton, Huntingdon, Cambs., PE17 0DA, England). *J Gen Virol* 38(1): 61-74; 1977.

Three inbred chicken lines (Reaseheath C, HPRS-synthetic, and RPRL-7-2) were used to study the relationship between the genes that regulate the antigenic expression of the subgroup E endogenous virus and those that control susceptibility to infection with exogenous viruses of subgroups A, B, and E. The tumor virus *e* (*tve*) and group-specific (*gs*) antigen loci are linked, as shown by the nonrandom association between the genes at the two loci. However, genes at *tva*, *tvb*, and *gs* segregate and recombine independently in accordance with Mendel's second law. *Tvb* and *tve* were also found to be two independently segregating loci, even though *tve* is linked to the *gs* locus. These findings suggest that the *gs* locus could be used as a marker for detecting the *tve* locus in chicken lines that lack the *Ie* gene. Contrary to a previous hypothesis, it is shown that the *Ie* gene is not identical to the *gs*+ gene. (36 refs.)

8-1555 **Antibody to Virion Structural Proteins in Mammals Bearing Avian Sarcoma Virus-induced Tumors.** (Eng) Brugge, J. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Erikson, E.; Erikson, L. *Virology* 84(2): 429-433; 1978.

The production of antibody to virion structural proteins was examined in rabbits and hamsters bearing tumors induced by avian sarcoma virus (ASV). Antibody activity was analyzed by the immunoprecipitation of polypeptides from radiolabeled ASV virions. Antipolymerase and antiglycoprotein activities were monitored by inhibition of the enzyme activity of virion polymerase and by neutralization of focus formation by group D ASV, respectively. Sera from rabbits bearing ASV-induced primary tumors contained antibody to all of the structural proteins of ASV, including the group-specific (*gs*) antigens, polymerase, and the membrane glycoprotein, gp85. Sera from hamsters bearing primary tumors contained detectable antibody to the *gs* antigens only. However, most sera from hamsters bearing tumors induced by injection of cloned hamster tumor cells displayed anti-*gs* activity, and some sera also exhibited antipolymerase activity. Although the presence of antibody to viral proteins in sera from tumor-bearing animals strongly suggests that the tumor cells are producing these proteins, the absence of detectable antibody does not necessarily imply that the proteins are not synthesized in the tumor cells. The absence of detectable antibody to gp85 and

polymerase in sera from hamsters bearing primary tumors could be related to the processing of these antigens or to the immunological response of the hamster. (9 refs)

78-1556 **Decreased Alkaline Phosphatase in Cells Transformed by Rous Sarcoma Virus.** (Eng) Bader, A. V. (Genetics Program, Natl. Inst. General Medical Sciences, NIH, Bethesda, MD 20014); Kondratick, J.; Bader, J. P. *Cancer Res* 38(2): 308-312; 1978.

Alkaline-phosphatase activity was examined in chick embryo cells transformed by either the Bryan high titer strain or the Schmidt-Ruppin strain Rous sarcoma virus (RSV) and in rat embryo cells transformed with Moloney sarcoma virus (MSV). All of the transformed cells had low levels of alkaline phosphatase activity compared with nontransformed cells. No differences in acid phosphatase activity were seen between these transformed and nontransformed cells. In studies with a temperature-dependent virus mutant, RSV-BH-Ta, enzyme activities were low in chick embryo cells maintained at the transformation-permissive temperature (37C) and high in cells maintained at the transformed-nonpermissive temperature (41C). Acid phosphatase levels were similar at the two temperatures. These results suggest that decreased alkaline phosphatase activities may be a general property of transformed cells. (22 refs.)

78-1557 **Increased Membrane Transport of 2-Deoxyglucose and 3-O-Methylglucose Is an Early Event in the Transformation of Chick Embryo Fibroblasts by Rous Sarcoma Virus.** (Eng) Lang, D. R. (Dept. Microbiology, Univ. Cincinnati Coll. Medicine, Cincinnati, OH, 45267); Weber, M. J. *J Cell Physiol* 94(3): 315-319; 1978.

Transport of 2-deoxyglucose and 3-O-methylglucose was examined in chicken embryo fibroblasts infected with a temperature-sensitive mutant NY-Ts68 of Rous sarcoma virus (RSV). Cells infected with this mutant are phenotypically normal at 42 C, but they are transformed rapidly and reversibly when the temperature is shifted to 36 C. Uptake of the two glucose analogs increased rapidly following a shift from 42 to 36 C, and it reached levels characteristic of fully transformed cells in approx 9 hr. Cells held at 36 C and shifted to 42 C showed a rapid decrease in glucose uptake and displayed transport rates characteristic of normal, uninfected cells within 6 hr. Uptake of the phosphorylated and nonphosphorylated forms of 2-deoxyglucose in normal cells and cells transformed by the Schmidt-Ruppin strain of RSV was also studied. There was a corresponding increase in the accumula-



tion of the free sugar in the transformed cells. The data point to transport as the rate limiting step in the accumulation of 2-deoxyglucose in both normal and transformed chicken embryo cells. Thus, increase in hexose transport in RSV-infected chicken embryo cells is an early event in transformation. (12 refs)

- 78-1558 In Vitro Translation of a 180,000-Dalton Rous Sarcoma Virus Precursor Polypeptide Containing Both the DNA Polymerase and the Group-specific Antigens.** (Eng) McGinnis, J. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710); Hizi, A.; Smith, R. E.; Leis, J. P. *Virology* 84(2): 518-522; 1978.

Translation of 34S RNA from the Prague C strain of Rous sarcoma virus (RSV Pr-C) in a Kreb's ascites cell-free protein-synthesizing system led to the synthesis of three detectable viral precursor polypeptides with electrophoretic mobilities corresponding to mol wt of 180,000, 70,000, and 65,000 daltons. The 180,000-dalton protein was precipitated by antiserum directed against purified B77 avian sarcoma virus reverse transcriptase as well as by serum against AMV group-specific (gs) antigens, but it was not precipitated by serum directed against RSV Pr-C gp85. The 70,000- and 65,000-dalton proteins were precipitated by antiserum directed against gs antigens, but not by antisera directed against polymerase, Friend murine leukemia virus p30, or RSV Pr-C gp85. Competition experiments with purified polymerase and gs antigens indicated that the 180,000-dalton protein has separate determinants for the gs antigens and polymerase. These conclusions were supported by preliminary tryptic mapping of the 180,000-dalton polypeptide, which was shown to contain tryptic peptides derived from the gs antigens and the polymerase. (30 refs)

- 78-1559 Tumor-Specific Surface Antigens on Rat Cells Transformed by Rous Sarcoma Virus.** (Fre) Laurent, J. C. (Unite de Virologie fondamentale et appliquee, I.N.S.E.R.M. U. 51, Group de Recherche 33, C.N.R.S., 1, place du Professeur-Joseph-Renaut, 69371 Lyon Cedex 2, France); Aupoix, M.; Greenland, T.; Krsmanovic, V. *C R Acad Sci [D] (Paris)* 285(16): 1599-1602; 1977.

A tumor-specific surface antigen (TSSA) was detected on rat cells transformed by Rous sarcoma virus (RSV, Prague strain, subgroup C). The cells were washed in phosphate-buffered saline and lysed by a detergent. The culture medium was centrifuged at 100,000 g and then precipitated with an ammonium sulfate soln in order to obtain the TSSA. Polyacrylamide gel electrophoresis of the cell membrane samples indicated that the antigen has a mol wt of 42,000. A mixed hemadsorption reaction with anti-TSSA antiserum was used to prove the presence of the TSSA. Target cells used in the hemadsorption reaction were RSV-transformed rat or ham-

ster cells or BHK21 or FEP nontransformed cells. Only the transformed cells inhibited the reaction. (9 refs)

- 78-1560 Inhibition of Rous Sarcoma Virus Replication and Cell Transformation by a Specific Oligodeoxynucleotide.** (Eng) Zamecnik, P. C. (John Collins Warren Labs., Huntington Memorial Hosp. Harvard Univ., Massachusetts General Hosp., Boston, MA, 02114); Stephenson, M. L. *Proc Natl Acad Sci USA* 75(1): 280-284; 1978.

In chick embryo fibroblast cultures infected with Rous sarcoma virus (RSV), virus production was inhibited by the addition of the tridecamer d(A-A-T-G-G-T-A-A-A-T-G-G) which is complementary to 13 nucleotides of the 3'- and 5'-reiterated terminal sequences of RSV 35S RNA. As measured by reverse transcriptase activity in the presence of 1 µg/ml of the tridecamer, the greatest inhibition (99%) occurred at the lowest multiplicity of virus infection (0.002). It is postulated that the tridecamer and its counterpart which blocked 3'- and 5'-hydroxyl termini entered the fibroblast cells, hybridized with the terminal reiterated sequences at the 3' and 5' ends of the 35S RNA, and interfered with one or more steps involved in viral production and cell transformation. The likely sites of action are (1) the circularization step of the proviral DNA intermediate and (2) the initiation of translation. (19 refs)

- 78-1561 Inhibition of Rous Sarcoma Viral RNA Translation by a Specific Oligodeoxyribonucleotide.** (Eng) Stephenson, M. L. (John Collins Warren Labs., Huntington Memorial Hosp. Harvard Univ., Massachusetts General Hosp., Boston, MA, 02114); Zamecnik, P. C. *Proc Natl Acad Sci USA* 75(1): 285-288; 1978.

In a cell-free wheat embryo system, translation of the 70S RNA's of Rous sarcoma virus (RSV) and avian myeloblastosis virus (AMV) was effectively inhibited by a tridecamer oligodeoxynucleotide, d(A-A-T-G-G-A-A-A-T-G-G) complementary to reiterated 3'- and 5'-terminal nucleotides of RSV 35S RNA. The inhibition was greater for the oncornavirus RNA's than for rabbit reticulocyte messenger RNA or brome mosaic virus RNA. Other oligodeoxynucleotides of similar size had little or no specific effect on the RSV directed translation. The tridecamer acted as a primer for RSV AMV DNA polymerase when heated RSV 70S RNA was used as a template, which indicates that it can hybridize to the RNA. (22 refs)

- 78-1562 Quantitation and Localization of Rous Sarcoma Virus-specific RNA in Transformed and Nontransformed Field Vole Cells.** (Eng) Krzyzek, R. A. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN)



55); Lau, A. F.; Vogt, P. K.; Faras, A. J. *J Virol* 25(2): 526; 1978.

Hybridization analysis of RNA from transformed clones of Rous sarcoma virus (RSV)-infected field vole cells and revertant subclones indicated that both cell types contained similar amounts of viral-specific RNA. Through the use of a relative-norm and representative complementary DNA probe of genome-length complementary DNA, it was demonstrated that the majority of RSV proviral DNA was transcribed as a virus-specific RNA in both transformed and revertant cells. The virus-specific RNA was present in several sizes, the largest of which was genome-length 35S RNA. Studies of the intracellular distribution of the virus-specific RNA indicated that it was present in the cytoplasm of transformed and revertant cells. Furthermore, the bulk of virus-specific nucleotide sequences were also associated with ribosomes in both cell types. These data indicate that the RSV provirus DNA is transcribed similarly into viral RNA in both transformed and revertant vole cells. Based on these results and previously demonstrated similarities in sarcoma-specific viral RNA in revertant and transformed vole cells, the loss of the transformed phenotype does not reflect changes in transcription of all or part of the RSV provirus or the processing, transport, or polyribosome association of virus-specific RNA representing the entire RSV genome. (31 refs)

78-1563 **Homology Between RNA's from Chicken Rous Sarcoma Cells and Rous Sarcoma Virus.** (Rus) Shoshnikov, Ia. D. (Lab. Biochemistry, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Ratovitskii, E. A.; Kuznetsov, O. K. *Biull Eksp Biol Med* 85(3): 332-334; 1978.

The possible homology between RNA preparations derived from chicken Rous sarcoma cells and Rous sarcoma virions was studied by an RNA-RNA molecular hybridization assay. <sup>125</sup>I-labeled RNA from virus mitochondria and membrane-bound polysomes showed 11.8% and 4.8% hybridization, respectively, with the RNA from Rous sarcoma cells. (1 ref)

78-1564 **Altered Glycosylhydrolase Activities in Virus Transformed Fibroblasts Related to Membrane Glycoprotein Structure (Meeting Abstract).** (Eng) Santer, U. (Dept. Pediatrics, Univ. Pennsylvania Medical Sch., Philadelphia, PA, 19104); Glick, M. C. *Proc Am Assoc Cancer Res* 181; 1978. (1 ref)

78-1565 **Effect of RSV Transformation on CEF Membrane Proteins (Meeting Abstract).** (Eng) Le-

Grue, S. (Univ. Texas Medical Sch., Houston, TX); Noll, H. *Proc Am Assoc Cancer Res* 19: 138; 1978. (no refs)

78-1566 **Radioimmunoassay for the Envelope Glycoprotein of Subgroup E Avian Leukosis-Sarcoma Viruses.** (Eng) Smith, E. J. (U.S. Dept. Agriculture, ARS, Regional Poultry Res. Lab., 3606 E. Mount Hope, E. Lansing, MI, 48823); Crittenden, L. B.; Whitson, A. K. *Virology* 84(2): 331-340; 1978.

The envelope glycoprotein of subgroup E avian leukosis virus (gpE) was purified from Rous-associated virus type 0 (RAV-0) and used in double-antibody competition radioimmunoassays (RIA) and radioimmune precipitations (RIP). When embryo extracts from various inbred lines of chickens were tested, the results of assays for chick helper factor (chf) and RAV-0 were in complete phenotypic agreement with those of RIA for gpE. The expression of genes at the *gs* and *gp* loci varied among inbred lines. Normal line 15I<sub>1</sub> embryos contained gpE but not group-specific (gs) antigens, but extracts from virus-free lines 15<sub>1</sub> and 6<sub>1</sub> contained both classes of antigen. Line 15B embryo extracts were negative for both gpE and gs antigen. Soluble gpE was found in sera of all chf-positive chickens from RAV-0-free lines. Sera from adult line 15B birds were categorized as: (1) positive for RAV-0 but negative for antibody; (2) negative for RAV-0 but positive for gpE and antibody to gpE; and (3) negative for RAV-0, antibody to gpE, and gpE. Evidence of antibody production was completely correlated in RIP of iodinated gpE and serum neutralizations of subgroup E virus. Results of RIP and gpE RIA indicated that half of the sera from nonviremic line 15B chickens contained antibodies to gpE as well as gpE. These findings indicate that the RIA for gpE can be used instead of the cell-culture assay for chf in the phenotypic classification of cells and lines. (38 refs)

78-1567 **Susceptibility of Avian Oncogenic Viruses: Determination of the Phenotype of Chickens.** (Fre) Stanislawski, L. (Laboratoire de Medecine Experimentale, U 112 de l'Institut national de la Sante, 75231 Paris Cedex 05, France); Teutsch, B.; Rabotti, G. F. *C R Acad Sci [D] (Paris)* 285(16): 1569-1572; 1977.

A great variability has been observed in the titer of antibodies to tumor-specific (ts) and group-specific (gs) antigens produced in chickens inoculated with the different strains of Rous sarcoma virus (RSV) or avian leukosis virus. It is hypothesized that the antiviral immune response is determined by the susceptibility or resistance of the chicken to the viral subgroups. Host susceptibility was determined in vitro by measuring the focus formation of fibroblasts from the pin feathers of 8- and 30-day-old ELB chicks after the cultured fibroblasts were infected with various RSV subgroups (RAV-1, Pr-RSV, RSV-Chf, Sr-RSV). The phenotypes of the chick-



ens were C/O, C/E, and C/BE. The method permitted study of the influence of host phenotype (susceptibility or resistance) on the immune response of the chicken to an RSV subgroup. (6 refs)

**78-1568 Thymectomy and Possible Bursectomy Increase Mortality in Marek's Disease (Meeting Abstract).** (Eng) Lam, K. M. (Temple Univ., Philadelphia, PA, 19140); Linna, T. J. *Fed Proc* 37(3): 412; 1978. (no refs)

**78-1569 Cyclophosphamide Induced Sensitivity Against Avian RNA Myeloblastosis Virus in Age-resistant Hosts.** (Eng) Smida, J. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Smidova, V. *Neoplasma* 24(6): 595-600; 1977.

The effect of cyclophosphamide administration on the survival of 4- to 7-wk-old chickens as well as on the induction of leukemia after injection of avian myeloblastosis virus (AMV) was studied. The drug treatment alone (75, 120, or 150 mg/kg/day ip for 5 consecutive days) had no neoplastic effect on the birds during 4 mo of observation. Immediate injection of AMV to cyclophosphamide-treated chickens induced acute myeloblastic leukemia in 80% of the challenged animals, but control chickens were resistant to infection. However, when AMV was injected 3 or 10 days after cyclophosphamide injection, a rapid and pronounced increase of resistance was observed. These results indicate the importance of cyclophosphamide treatment in overcoming the age-dependent resistance of old chickens to AMV infection. (15 refs)

**78-1570 Protein Kinase from Avian Myeloblastosis Virus.** (Eng) Houts, G. E. (Dept. Chemistry, Univ. Montana, Missoula, MT, 59801); Miyagi, M.; Ellis, C.; Beard, D.; Watson, K. F.; Beard, J. W. *J Virol* 25(2): 546-552; 1978.

A protein kinase associated with purified virions of avian myeloblastosis BAI strain A was purified and characterized. The enzyme had an isoelectric point of 9.3 and a mol wt of 45,000. The transfer of phosphate catalyzed by this enzyme required a divalent metal ion and ATP as a phosphate donor. Beef heart protein kinase inhibitor and cyclic AMP had no effect on the reaction. Only acidic proteins could be phosphorylated. (27 refs)

**78-1571  $\beta$ -Lapachone, an Inhibitor of Oncornavirus Reverse Transcriptase and Eukaryotic DNA Polymerase- $\alpha$ . Inhibitory Effect, Thiol Dependency and**

**Specificity.** (Eng) Schuerch, A. R. (Biological Res. Labs. Pharmaceuticals Div., Ciba-Geigy Ltd., Basel, Switzerland); Wehrli, W. *Eur J Biochem* 84(1): 197-205; 1978.

$\beta$ -Lapachone, a naturally occurring compound that can be isolated from a number of tropical trees, was a potent inhibitor of reverse transcriptase activity from avian myeloblastosis virus and Rauscher murine leukemia virus. In addition, it affected eukaryotic DNA-dependent DNA polymerase- $\alpha$  activity: an 8  $\mu$ M concentration resulted in 50% inhibition after a 60-min incubation period. The inhibitory effect of  $\beta$ -lapachone did not depend on enzyme purity or on the amount or type of template primer and substrate. However, inhibition of viral reverse transcriptase occurred only in the presence of dithiothreitol. The primary site of action of the drug appears to be the enzyme protein, as evidenced by the specificity of its action. Eukaryotic DNA-dependent DNA polymerase  $\beta$ , prokaryotic DNA-dependent DNA polymerase I, several other nucleic acid polymerases, and some completely unrelated enzymes were not affected. Reverse transcriptase and DNA-dependent DNA polymerase- $\alpha$  may be related in possessing similarly exposed -SH structures in their active sites.  $\beta$ -Lapachone affords a novel means of studying such interrelationships and of further characterizing the enzymes. (5 refs)

**78-1572 Deposition of Retrovirus Associated Antigen (p30 and gp70) on Cell Membranes of Feline and Murine Leukaemia Virus Infected Cells.** (Eng) O'Brien, S. J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Simonson, J. M.; Davis, S. *J Gen Virol* 38(3): 483-496; 1978.

The number of retrovirus-associated cell-membrane antigens of murine and feline cells infected with their respective C-type leukemia viruses was quantitated. The minimum estimate number of retrovirus-associated antigenic determinants on YAC [Moloney leukemia virus (MuLV)-infected murine] and FL-74 [feline leukemia virus (FeLV)-infected feline] cells was  $1.3 \times 10^6$  and  $1.6 \times 10^6$  determinants per cell, respectively. The virus structural proteins p27-30 and gp70 were detected by three component-specific antisera on murine and feline cell surfaces in amounts that varied with cell isolates. MuLV infected cells produced as many as  $1.9 \times 10^5$  p30 antigenic determinants and  $7.5 \times 10^5$  gp70 determinants on infected cells. FeLV-infected cells (FL-74) expressed  $5.6 \times 10^5$  p27 and  $7.5 \times 10^5$  gp70 antigenic determinants per single cell surface. The major core protein (p27-30) and the major envelope glycoprotein (gp70) antigens were sufficiently physically separated on the cell surfaces so that binding of either of the membrane antigens with component-specific antibodies did not interfere with binding of antibodies specific for the other. Despite the expression of interspecies determinants for p30, gp70, and the other retrovirus-associated antigens detected by antibody procedures, interspecies determinants of cell-mediated immunity could not be demonstrated in immunized



mice bearing Moloney sarcoma virus (MSV)-induced tumors. Furthermore, xenogeneic immunization of mice with FL-74 cells failed to protect mice against the growth of MSV-induced lymphoma or sarcoma. (46 refs)

**78-1573 An Analysis of Type-C Retrovirus Polypeptides and Their Associations in the Virion.** (Eng) Montelaro, R. C. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710); Sullivan, S. J.; Bolognesi, D. P. *Virology* 84(1): 19-31; 1978.

The polypeptide composition of <sup>3</sup>H-leucine-labeled Rous sarcoma virus, subgroup C (Pr-RSV-C), and Friend murine leukemia virus (FLV) was determined by guanidine hydrochloride gel filtration and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. These techniques resolved seven major structural components of Pr-RSV-C (gp85, gp35, p27, p19, p15, and p10), as reported previously for other avian leukosis-sarcoma viruses. For FLV, however, two previously unresolved proteins (P15E and P12E) were demonstrated in addition to gp71, p30, p15C, p12, and p10. FLV p15E, p12E, and gp71 were removed when intact virions were digested with bromelain, which suggests that these proteins are located on the virion surface. Polypeptide linkage studies indicated that >90% of avian gp85 and gp35 are disulfide-linked as a viral glycoprotein complex (VGP). Avian p19 appeared to exist as a network of disulfide-linked molecules, some of which contained additional linkages to the VGP. In contrast to the avian system, only 10%-15% of FLV p15E was disulfide linked to p15C in the VGP; the remaining p15E was loosely attached to the virus, possibly by a noncovalent interaction with p12E. (34 refs.)

**78-1574 Immunization Patterns with Friend Leukemia Virus (FLV), a Sarcoma Pseudotype (MSV-F) and a FV Vaccine (Meeting Abstract).** (Eng) Basombrio, M. (Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Melo 3081, 1425 Buenos Aires, Argentina); Mayer, A. M. *Proc Am Assoc Cancer Res* 19: 40; 1978. (no refs)

**78-1575 Alterations in the Protein Synthetic Apparatus of Friend Erythroleukemia Cells Infected with Vesicular Stomatitis Virus or Herpes Simplex Virus.** (Eng) Shioka, Y. (Dept. Microbiology, Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032); Silverstein, J. *J Virol* 25(1): 422-426; 1978.

The effects of herpes simplex virus (HSV) and vesicular stomatitis virus (VSV) infection on cellular messenger RNA's (mRNA's) in Friend erythroleukemia (FL) cells were investi-

gated. Although previous studies indicated that HSV infection shuts off the synthesis of globin and other cellular polypeptides, globin synthesis persisted in FL cells infected with VSV. Physical measurements of the size of bulk-infected cell mRNA demonstrated that there was no detectable change in the size of the mRNA's after infection with VSV. The hybridization kinetics of cytoplasmic RNA extracted from cells infected with HSV or VSV were compared with globin complementary DNA. By 4 hr postinfection with HSV, only about 15% of the globin mRNA sequences remained, but there was no detectable change in the sequence abundance of globin mRNA in the VSV-infected cells. Therefore, there must be a selective translation control that permits VSV and mRNA to be translated without increasing the amount of ribosomes present as polyribosomes. Hence, degradation of cellular mRNA appears to be a unique consequence of HSV infection. (32 refs.)

**78-1576 Distribution of the Globin Gene in Active and Inactive Chromatin Fractions from Friend Erythroleukemia Cells.** (Eng) Lau, A. F. (Dept. Microbiology, Univ. Minnesota, Minneapolis, MN, 55455); Ruddon, R. W.; Collett, M. S.; Faras, A. J. *Exp Cell Res* 111(2): 269-276; 1978.

Changes in the content of the globin gene sequences were examined in the T3C12 clone of Friend murine erythroleukemia cells, which accumulate globin messenger RNA (mRNA) after stimulation by dimethyl sulfoxide (DMSO). There was a progressive increase in the concentration of globin mRNA sequences in the total cellular RNA of the DMSO-treated cells, as measured by nucleic acid hybridization using a globin complementary DNA (cDNA) probe. The greatest increment in the content of globin RNA occurred 30-40 hr after addition of the DMSO. Equal concentrations of globin sequences were present in the DNA isolated from active and inactive chromatin fractions of cells grown in the presence of 1.2% DMSO for 50 hr (the time of initiation of Hb synthesis). There were no significant differences in the globin gene concentrations between the active chromatin fractions from DMSO-treated and control cultures at 50 or 120 hr after initiation of DMSO treatment. However, chromatin-associated RNA isolated from the active chromatin of cells synthesizing maximum amounts of Hb (120 hr) contained a higher concentration of globin sequences than RNA from the active chromatin of control cells. Chromatin fractions from untreated cells also contained a significant amount of RNA that hybridized to the globin cDNA probe. These findings suggest that both transcriptional and posttranscriptional control mechanisms are involved in Hb gene expression in T3C12 erythroleukemia cells. (40 refs)

**78-1577 Production of Friend Virus Particles on the Surface of Cells Synchronized by Ficoll Gradient**



**Centrifugation.** (Fre) Michel, M. L. (Laboratoire d'Hématologie expérimentale, Institut de Recherches sur les Maladies du Sang, Hôpital Saint-Louis, 2, place du Docteur-Fournier, 75010 Paris, France); Samso, A.; Larsen, C. J. *C R Acad Sci [D] (Paris)* 286(3): 297-300; 1978.

Murine cells of the STU line, which continuously produce Friend leukemia virus in vitro, were investigated to determine whether viral release is limited to particular phases of the cell cycle. The cells were incubated with triated thymidine and then synchronized by Ficoll gradient centrifugation. Cells were isolated from different fractions of the gradient and examined under an electron microscope. Counts of budding viral particles on the cell surface were performed on ultrathin cell sections and correlated with the rate of DNA synthesis. The number of budding viral particles did not vary significantly in the various phases of the cell cycle. However, the continuous release of virus throughout the cell cycle may not indicate continuous viral RNA synthesis: there may be intracellular reservoirs of the virus that are augmented by synthesis at certain phases of the cycle. (11 refs)

**78-1578 The Detection of a Spleen Focus Forming Virus (SFFV) Cell Surface Antigen by Lymphocyte-mediated Cytolysis (Meeting Abstract).** (Eng) Gillis, S. (Dartmouth Medical Sch., Hanover, NH, 03755); Gillis, A. E.; Smith, K. *Proc Am Assoc Cancer Res* 19: 236; 1978. (no refs)

**78-1579 Molecular Mechanisms of the Interaction Between Oncogenic Viruses and Host Cells.** (Rus) Zhdanov, V. M. (D. I. Ivanovsky Inst. Virology, Moscow, USSR); Altshtein, A. D. *Vestn Akad Med Nauk SSSR* (10): 59-64; 1977.

The content of provirus DNA was assessed in the spleen, placenta, and embryo cells of normal and Rauscher leukemia-bearing BALB/c mice. The extent of molecular hybridization of Rauscher leukemia virus <sup>3</sup>H-DNA with the DNA from leukemic spleen was 85%, compared with 52% with the DNA from normal spleen. The amount of virus-specific RNA in mice with Rauscher leukemia was almost 10 times greater than that in normal mice. Analysis of virus-specific RNA in three cell lines (XC, TWERC, and RVP,) transformed by Rous sarcoma virus showed that the XC line contained almost three times as much RNA as the two other lines. These data indicate that viral carcinogenesis is accompanied by the appearance of virus-specific nucleic acids in the transformed cells. (7 refs.)

**78-1580 Inhibition of Maturation of Rauscher Leukemia Virus by Amino Acid Analogs.** (Eng) Jamjoom, G. A. (Dept. Biology, Univ. Texas System Cancer Center,

M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Ng, V. L.; Arlinghaus, R. B. *J Virol* 25(1): 408-412; 1978.

The effect of canavanine (CV) and p-fluorophenylalanine (FPA) on the cleavage and release of virus particles from Rauscher leukemia virus-infected NIH Swiss mouse embryo fibroblasts was investigated. Although the primary precursor polypeptides of core and envelope viral proteins were synthesized in the presence of 4 mM CV and 4 mM FPA, cleavage of these precursors was inhibited severely. This treatment also depressed the release of characteristic virus or stable virus-like particles. The degree of inhibition and of virus release varied with the concentration of CV and FPA used. It is suggested that the inhibitors act directly on the cleavage reaction of the precursors, thus preventing the release of virus particles. Protein synthesis was also inhibited with these compounds, but low levels of arginine relieved the inhibitory effect of CV on protein synthesis. (21 refs.)

**78-1581 Separation of the Tumor Rejection Antigen (TSTA) from the Major Viral Structural Proteins of the Cell Membrane of an R-MuLV Induced Leukemia (Meeting Abstract).** (Eng) Rogers, M. J. (NCI, Bethesda, MD, 20014); Law, L. W.; Prat, M.; Oroszlan, S.; Appella, E. *Proc Am Assoc Cancer Res* 19: 62; 1978. (no refs)

**78-1582 Persistence of Sindbis Virus in Cultures Not Producing and Irregularly Producing Oncornavirus.** (Rus) Pogodina, V. V. (Inst. Poliomyelitis and Viral Encephalitis, Moscow, USSR); Kiseleva, L. L.; Miller, G. G.; Fokina, G. I.; Graevskaya, N. A.; Sito, A. F.; Ivanov, A. F. *Vopr Virusol* (1): 52-56; 1978.

Eight monolayers of BALB/c mouse embryo cells were infected with Rauscher leukemia virus (RLV) and Sindbis virus (SV) or SV alone. Each initial culture was subcultured every 7-10 days (34-36 passages), and the persistence of the oncovirus in successive subcultures was assessed. The culture initially infected with SV alone showed progressive loss of hemagglutinating and interferon-inducing activity. On day 68-82, the presence of virus could be detected only by immunofluorescence; on day 241, the culture developed resistance to superinfection with homologous virus. Similar features were observed in the culture infected with SV and RLV, although the homologous interferon to SV could be detected not on day 179 of culturing, as in the system infected with SV alone, but on day 40. (18 refs)

**78-1583 Studies on Fv-1 Restriction in N Type Mouse Cells (Meeting Abstract).** (Eng) Barlow, B. M.



584 Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Rein, R. H.; Rein, A. *Proc Am Assoc Cancer Res* 19: 40; (no refs)

584 Studies on the Mechanism of FV-1 Restriction with Heated MuLV's (Meeting Abstract). (Eng) van-Troise, G. (NCI, Bethesda, MD, 20014); Gerwin, B. *Proc Am Assoc Cancer Res* 19: 55; 1978. (no refs)

585 Lack of Correlation Between Expression of 'Amphotropic' MuLV and Oncogenicity (Meeting Abstract). (Eng) Beardsley, T. R. (Univ. California, Los Angeles, CA, 90024); Hays, E. F. *Proc Am Assoc Cancer Res* 145; 1978. (no refs)

586 Polymorphism in the Major Core Protein (p30) of Murine Leukemia Viruses as Identified by Mouse Antisera. (Eng) Boiocchi, M. (Divisione Oncologia Sperimentale A, Istituto Nazionale Tumori, Via Venezian 1, Milan, Italy); Nowinski, R. C. *Virology* 84(2): 530-535; 1978.

Antisera prepared in C57BL/6 mice against AKR K36 leukemia cells detected group-specific and class-specific antigen-determinants on the major core protein (p30) of murine leukemia virus (MuLV). Sera that contained a predominance of antibodies against class-specific antigens reacted preferentially with the p30 proteins of ecotropic MuLV; these sera did not react with the p30 proteins of xenotropic MuLV. It is likely that the immune response of the mouse is directed only a minor portion of the p30 molecule, as tryptic peptide maps and quantitative immunological analysis of p30 demonstrated < 5% variation in the p30 proteins of ecotropic and xenotropic MuLV. (31 refs)

587 Role of Murine Leukemia Virus and H-2 Antigens on the Surface of Leukemia Cells in Immune Cell Mediated Lysis (Meeting Abstract). (Eng) Watson, A. (Univ. Wisconsin, Madison, WI, 53706); Zarling, J. E.; Bach, F. H.; Zarling, D. A. *Proc Am Assoc Cancer Res* 200; 1978. (no refs)

588 Virus-Related Alterations of Thymic Cell Architecture (Meeting Abstract). (Eng) Mariani, A. (Dept. Lab. Medicine-Pathology, Univ. Minnesota, Minneapolis, MN, 55455); Clawson, C. C.; Landucci, G. *Fed Proc* 33: 335; 1978. (no refs)

78-1589 Characterization and Mapping of RNase T1-resistant Oligonucleotides Derived from the Genomes of Akv and MCF Murine Leukemia Viruses. (Eng) Rommelaere, J. (Dept. Biology and Center Cancer Res., MIT, 77 Massachusetts Ave., Cambridge, MA, 02139); Fallender, D. V.; Hopkins, N. *Proc Natl Acad Sci USA* 75(1): 495-499; 1978.

<sup>32</sup>P-labeled 70S RNA's from Akv and MCF leukemia viruses were digested with RNase T1, and the resulting nucleotides were separated by two-dimensional gel electrophoresis. The T1 RNA fingerprints of the genomes of Akv-1 and Akv-2 viruses were indistinguishable and oligonucleotide maps of these viruses were similar. Akv-1 and -2 shared 55-75% of their large T1-resistant oligonucleotides with four MCF viruses isolated from AKR mice or from NIH Swiss mice that inherit either the Akv-1 or Akv-2 virus-inducing locus of AKR. The majority of Akv oligonucleotides missing from T1 fingerprints of MCF's and the majority of oligonucleotides unique to MCF viruses were clustered at corresponding positions in the 3' half of the oligonucleotide maps of the Akv and MCF viruses. The RNA sequences present in different MCF isolates but not in Akv viruses were related. These results are consistent with the proposed recombinational origin of MCF viruses. (15 refs)

78-1590 Equivalent Expression of Endogenous Murine Leukemia Virus-related Genes in C3H/10T(1/2) Cells and Chemically Transformed Derivative Cells. (Eng) Getz, M. J. (Dept. Pathology and Anatomy, Mayo Clinic and Mayo Foundation, Rochester, MN, 55901); Elder, P. K.; Moses, H. L. *Cancer Res* 38(3): 566-569; 1978.

Studies were conducted to determine whether chemical carcinogens induce enhanced expression of endogenous C-type RNA tumor virus genes in the absence of intact virus particle production. The concentration and diversity of murine leukemia virus (MuLV)-related RNA sequences associated with the polyribosome fraction of nontransformed C3H/10T(1/2) clone 8 cells and a 3-methylcholanthrene-transformed derivative clone, C3H/MCA-58, were determined by RNA-complementary DNA (cDNA) hybridization using a cDNA probe synthesized from purified MuLV 70S RNA. Although both clones are virus nonproducers, they contained significant amounts of polyadenylate-containing MuLV-related RNA sequences; the types and quantities of these sequences were indistinguishable in both clones. These results suggest that expression of the corresponding gene sequences into RNA is not related to the maintenance of the transformed state in these chemically transformed cells but appears to be dependent on the strain of the target cell. (21 refs)

78-1591 Prevalence of Non-T-Cells in the Replication of the N-Tropic, Type C Virus of Young AKR Mice. (Eng) Gisselbrecht, S. (Laboratoire d'Immunologie et



de Virologie des Tumeurs, INSERM U 152, Hopital Cochin, 27 rue du Faubourg Saint Jacques, 75674 Paris Cedex 14, France); Blaineau, C.; Hurot, M. A.; Pozo, F.; Levy, J. P. *Cancer Res* 38(4): 939-941; 1978.

The origin of the N-tropic C-type endogenous virus in AKR mice was investigated using the XC infectious center assay. A high number of nucleated spleen cells plaqued as infectious centers: usually  $> 10^3$  producers/million cells were found. However, the number of infectious centers was low in the thymus of 8- to 15-day-old mice: it was approx 100 times less than that in the spleen. Although the number increased slightly with age, it was rarely  $> 10^2$ /million thymus cells. Larger numbers of producer cells were found only in the thymuses of animals with generalized leukemia. In other experiments, deletion of T cells did not decrease the number of spleen cells plaquing as infectious centers, but when T-cell-enriched suspensions were used, a decrease in plaque formation was noted. In overtly leukemic mice, T-depleted and T-enriched suspensions plaqued equally well. It is suggested that the N-tropic murine leukemia virus of young AKR mice is produced mainly by non-T cells. (19 refs)

**78-1592 Translation of MuLV and MSV RNAs in Nuclease-Treated Reticulocyte Extracts: Enhancement of the gag-pol Polypeptide with Yeast Suppressor tRNA.** (Eng) Philipson, L. (Biomedical Center, Univ. Uppsala, Uppsala, Sweden); Andersson, P.; Olshevsky, U.; Weinberg, R.; Baltimore, D.; Gesteland, R. *Cell* 13(1): 189-199; 1978.

The virion RNA's from Moloney murine leukemia virus (MuLV) and Moloney murine sarcoma virus (MSV) were translated in a micrococcal nuclease-treated cell-free system from rabbit reticulocytes. The predominant polypeptides formed from 35S MuLV RNA were 78,000 (78K) and 65K daltons in mol wt; minor components of 180K, 110K, 52K, and 40K daltons were also observed. The 30S MSV RNA yielded two predominant polypeptides of 62K and 43K daltons and minor components of 72K, 40K, and 18K daltons. Immunoprecipitation with specific antisera indicated that the predominant polypeptides generated by both MuLV and MSV RNA were precursors of the core proteins. The 180K-dalton polypeptide encoded by MuLV RNA was immunoprecipitated by antisera to the core protein (p30) and reverse transcriptase. The major products therefore appear to be Pr65-gag and Pr78-gag; an important minor product is Pr180-gag-pol. When purified yeast suppressor tRNA was added to the translation mixture directed by 35S MuLV RNA, the amount of Pr78-gag was reduced, but that of Pr180-gag-pol was enhanced. This pattern of suppression was also seen for an established amber mutation (UAG) in the synthetase gene of bacteriophage Q $\beta$  (Q $\beta$  aml), suggesting that it is a UAG codon that terminates the synthesis of Pr78-gag. In the MSV system, the yeast suppressor tRNA increased the synthesis of the 72K-dalton polypeptide and slightly reduced the 62K-dalton protein. These results sug-

gest that a suppression mechanism may control the relative amounts of core protein and reverse transcriptase synthesized from 35S mRNA. (43 refs)

**78-1593 Electron Microscopic Studies of Intracisternal Virus Particles in Soehner-Dmochowski Murine Sarcoma Virus-induced Bone Tumors of New Zealand Black Rats.** (Eng) Ohtsuki, Y. (Dept. Pathology, Okayama Univ. Medical Sch., Okayama, 700 Japan); Dmochowski, L. Seman, G.; Bowen, J. M. *Cancer Res* 38(4): 901-906; 1978

Intracisternal virus particles were detected in Soehner-Dmochowski murine sarcoma virus (Moloney) [SD-MSV(M)]-induced bone tumors in New Zealand Black rats, and they were characterized morphologically and immunologically. The virus particles, 90-120 nanometers in diameter, were found in the rough endoplasmic reticulum. They had two inner concentric layers with a relatively electron-lucent center, frequently showing cylindrical, chainlike, or multipolar budding forms. Extracellular C-type virus particles were also detected in these tumors. In addition, both types of virus particles were observed in tissue culture cells from normal prostate tissues of A/Dm and BALB/c/Dm mice after they were infected with cell-free extracts of the SD-MSV(M) tumors. The C-type virus particles in the prostate tissue culture cells belonged to the murine sarcoma-murine leukemia virus group, as revealed by the fixed immunofluorescence test and by immunoelectron microscopy. Morphological and immunological studies showed that the observed intracisternal virus particles were different from intracisternal type-A, -H, or -R particles; extracellular type-C particles; and intracisternal virus particles in guinea pig leukemia. (29 refs)

**78-1594 Relationship Between Moloney MSV Tumor Resistance and Endogenous Virogene Expression in AKR Mouse Strain and Its Hybrids.** (Eng) Colombatti, A. (Biological Dept., Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, Netherlands); De Rossi, A.; Taylor, B. A.; Chicco-Bianchi, L.; Meier, H. *Int J Cancer* 21(2): 179-185; 1978.

The induction of Moloney murine sarcoma virus (M-MSV) in AKR and other mouse strains was studied in relation to endogenous virus expression. M-MSV titers of  $6.5 \times 10^7$  or  $4.0 \times 10^7$  were diluted 1:2 or 1:3 and injected im into recipient mice. BALB/c, B10BR/SgSn, CBA, C57BL/6, C57L DBA/2, Swiss NIH, and FVB/N mice developed tumors only AKR mice did not. Furthermore, only AKR mice were producers of murine leukemia virus (MuLV). The selectivity of MSV tumor resistance was associated with AKR virogene segregation in the first backcross to MuLV-negative/MSV-susceptible mice and in a few second backcross families. These mice, mice congenic for the *Akv-2* viral gene, and recombinant inbred strains derived from an original cross



AKR and C57L mice inherited not only the endogenous viral genes, but also the ability to show strong resistance to tumor induction by an exogenous oncogenic virus. This suggests that ecotropic endogenous viruses can provide some protective functions to the host. However, the mechanism by which MuLV + mice are refractory to M-MSV infection is unknown. (26 refs)

**78-1595 Epithelioid and Fibroblastic Rat Kidney Cell Clones: Epidermal Growth Factor (EGF) Receptors and the Effect of Mouse Sarcoma Virus Transformation.** (Eng) De Larco, J. E. (Lab. Viral Carcinogenesis, NIH, Bethesda, MD, 20014); Todaro, G. J. *J Cell Biol* 94(3): 335-342; 1978.

Epithelioid and 17 fibroblastic clones from normal rat kidney were isolated and studied for their ability to bind epidermal growth factor (EGF), susceptibility to transformation by Moloney murine sarcoma virus, and alteration in EGF binding upon virus transformation. The epithelioid clones bound 64.3 femtomoles EGF per  $10^6$  cells and the fibroblastic clones bound 7.7 femtomoles EGF per  $10^6$  cells. Scatchard analysis on one epithelioid and one fibroblastic clone showed that the higher EGF binding was due to a greater number of receptors on the epithelioid cells rather than to a difference in the apparent affinity constant. Virus transformation decreased EGF binding, the effect being greater in the fibroblastic clones. In 20/20 independently isolated virus-transformed clones, the level of EGF binding was either greatly reduced or completely eliminated. Multiplication-stimulating activity, however, bound to a greater extent to fibroblastic clones than to epithelioid clones, and the binding was not decreased by sarcoma virus transformation. Thus, alteration of the EGF receptor appears to be a specific effect of murine sarcoma virus transformation. (29 refs)

**78-1596 Characterization of Tumour Virus Proteins. II. Expression of the Protein P30 in Transformed Productive and Non-productive Ki/NRK Cells.** (Eng) Higuera, T. (Instituto de Quimica, Universidade de Sao Paulo, Sao Paulo, SP, Brazil); August, J. T. *An Acad Bras Cienc* 49(2): 334-348; 1977.

Expression of the P30 structural protein of murine tumor virus was evaluated in nonproducer rat kidney cells transformed by Kirsten (Ki) sarcoma and leukemia viruses. Productively transformed and uninfected cells were used as controls. Competition assays in homologous antigen-antibody systems showed that the productive cells shared group- and virus-specific antigenic determinants with Rauscher leukemia virus (R-MuLV) and feline LV. These cells showed significant competition when assayed with Ki and R-MuLV antiserum against the R-MuLV P30. No P30 was detectable in the nonproducer cells, indicating that the

expression of this antigen is not correlated directly with transformation. (33 refs)

**78-1597 Histopathology and  $^{14}\text{C}$ -Pregnenolone Metabolism of Kirsten Murine Sarcoma Virus (Ki-MSV) Transformed Cultured Rat Adrenocortical Cells (Meeting Abstract).** (Eng) Auersperg, N. (Cancer Res. Centre and Dept. Zoology, Univ. British Columbia, Vancouver, B. C. V6T 1W5, Canada). *Proc Am Assoc Cancer Res* 19: 216; 1978. (no refs)

**78-1598 Isolation of Thioguanine Resistant Variants of K-BALB Cells Non-inducible for Type C Viruses by 5-Iododeoxyuridine.** (Eng) Aksamit, R. R. (Lab. Immunobiology, NCI, NIH, Bethesda, MD, 20014); Long, C. W. *J Gen Virol* 38(3): 419-429; 1978.

K-BALB mouse cells (BALB/c cells transformed by Kirsten sarcoma virus) selected in culture for 6-thioguanine resistance were isolated and characterized. These clones were inducible for endogenous C-type virus synthesis by cycloheximide and dexamethasone, but not 5-iododeoxyuridine. A comparison of the number of foci formed on NRK and SC-I cells suggested that the xenotropic virus was suppressed. The variants were not defective in the incorporation of thymidine or iododeoxyuridine or deficient in thymidine kinase, but they were deficient in hypoxanthine-guanine phosphoribosyltransferase and the incorporation of hypoxanthine into nucleic acid. Because these cells are blocked at some point in the expression of endogenous virus, they may prove useful in establishing the mechanisms involved in chemical activation of virus synthesis. (28 refs)

**78-1599 Growth Enhancement of Murine Sarcoma by LDH-Virus, Adrenocorticoids, and Anxiety Stress (Meeting Abstract).** (Eng) Riley, V. (Pacific Northwest Res. Foundation, Seattle, WA, 98104); Spackman, D. H.; Hellstrom, K. E.; Hellstrom, I. *Proc Am Assoc Cancer Res* 19: 57; 1978. (no refs)

**78-1600 Ring-shaped Structures and Virus like Particles.** (Ger) Heine, H. (Anatomisches Institut der Universität Würzburg, Koellikerstrasse 6, D-8700 Würzburg, W. Germany); Schaeg, G.; Nasemann, T. *Arch Dermatol Res* 260(3): 241-246; 1977.

The decidual cells of normal mouse placenta were examined by electron microscopy, and their morphology was compared with that of several virus preparations. Ring-shaped structures resembling virus particles were found in the cell mem-



branes of the mouse cells. The appearance of these particles depended on the direction in which tissue specimens were sectioned. Many of the viruslike particles described in tumor research may, in fact, be these ring-shaped structures. (8 refs)

- 78-1601 Mitogen Induction of Murine C-Type Viruses. IV. Effects of Lipoprotein *E. coli*, Pokeweed Mitogen and Dextran Sulphate.** (Eng) Moroni, C. (Friedrich Miescher-Institut, CH-4002 Basel, Switzerland); Schumann, G. *J Gen Virol* 38(3): 497-503; 1978.

Induction of murine C-type viruses by lipoprotein *Escherichia coli* (LP), pokeweed mitogen (PWM), and dextran sulfate (DS) was studied to determine how B-cell mitogenicity is correlated with virus induction. Spleen cells were obtained from specific pathogen-free BALB/c, AKR, and nu/nu mice. LP, in concentrations of 5 and 50 µg/ml, was an inducer of endogenous C-type virus from BALB/c mouse spleen cells; addition of 5 µg/ml 5-bromo-2'-deoxyuridine (BUdR) enhanced virus release. The induced virus had both the characteristic density and morphology of C-type viruses, and budding viruses could be detected electron microscopically 2-4 days following culture in the presence of LP. PWM (16 µg/ml) had a mitogenic effect on BALB/c and nu/nu spleen cells and BALB/c cortisone-resistant T cells, but it did not induce C-type virus either alone or in combination with BUdR. DS (20 µg/ml) did not induce C-type virus alone. When it was tested with lipopolysaccharide (LPS; 16 µg/ml), purified protein derivative (PPD; 50 µg/ml), or concanavalin A (Con A; 4 µg/ml), a synergistic effect was observed with LPS, inhibition with PPD and Con A. These results were also observed in cultures containing BUdR. Combinations such as LPS + PPD and LPS + Con A did not show additive effects and were, in fact, inhibitory. (15 refs)

- 78-1602 Expression of Oncornavirus C-Type Proteins in Tumors in CC57BR Mice.** (Rus) Bogovskii, B. P. (Lab. Immunochimistry and Tumor Diagnosis, Cancer Res. Center, Moscow, USSR); Lezhneva, O. M. *Biull Eksp Biol Med* 85(3): 334-337; 1978.

Expression of the endogenous murine oncornavirus C-type genome was studied in methylcholanthrene (MC)-induced tumors in CC57BR mice. The 4 to 6-wk-old mice were inoculated sc with MC (0.3 mg in 0.1 ml of peach oil). Approx 20 wk later, 14/39 mice developed sc sarcomas. When the tumors reached 15-20 mm in diameter, they were removed; part of the tumor tissue was transplanted sc into mature CC57BR mice, and the remainder was used for the preparation of antigen extracts. The presence of virus genome markers, group-specific antigen gs-1 and Gross leukemia virus antigen (GLVA), was assessed by radioimmunodiffusion assay. Of 14 primary MC-induced sarcomas, 13 contained gs-1, but only 1 contained GLVA. Successive passages markedly increased

the titer of gs-1; this increase was correlated with the presence of GLVA. (13 refs)

- 78-1603 Endogenous Type-C Viruses: Expression and Cellular Differentiation (Meeting Abstract).** (Eng) Canivet, M. (Laboratoire d'Hématologie Experimentale, Hopital Saint-Louis, Paris, France); Emanoil-Ravicovitch, R.; Robert, J.; Peries, J.; Boiron, M. *Proc Am Assoc Cancer Res* 19: 169; 1978. (no refs)

- 78-1604 Spontaneous Expression of Endogenous Type C RNA Virus by BALB/c Splenic B Lymphocytes in Continuous Culture.** (Eng) Premkumar-Reddy, E. (Microbiological Associates, 5221 River Road, Bethesda, MD, 20014); Price, P. J.; Heilman, C. J.; Sarma, P. S. *Virology* 84(2): 341-347; 1978.

B-lymphocyte cultures were established from spleens of BALB/c, C57Bl/6, NIH Swiss, and SWR mice of various ages. The culture supernatants were assayed for RNA-dependent DNA polymerase activity from the very first passage to test whether any of the cultured B lymphocytes spontaneously expressed C-type viruses. Spontaneous, consistent release of a B-tropic mouse endogenous C-type virus occurred from the first passage in cultured lymphocytes from BALB/c mice 6 mo old or older, but not from similar lymphocytes derived from BALB/c mice of 1.5 or 3 mo of age. C57Bl/6, NIH Swiss, and SWR mice ranging in age from 1.5 to 18 mo did not exhibit such a spontaneous release of viral particles. It is concluded that in BALB/c splenic lymphocytes, a breakdown of cellular control mechanisms occurs in older animals, leading to viral production, but such a phenomenon is absent in C57Bl/6, NIH Swiss, and SWR mice. This finding may be related to the fact that the incidence of neoplasms increases with age in BALB/c mice but neoplasms are rare in the other three species, even in older animals. (31 refs)

- 78-1605 Polypeptides of Lactate Dehydrogenase Isoenzymes in the Mammary Tissue of C<sub>3</sub>H Mice with Bittner's Tumor (MMT).** (Spa) Carda Aparici, P. (Departamento de Inmunopatología, Instituto Nacional de Oncología, Ciudad Universitaria, Madrid-3, Spain); Diaz Yubero, M.; Perez Cuadrado, S. *Rev Esp Oncol* 24(1): 1-22; 1977

Mammary tissue lactate dehydrogenase LDH isoenzymes were studied in 50 C3H mice divided into five groups of 10 animals each. Ninety percent of the females of this strain developed mammary gland adenocarcinoma (Bittner's tumors) after the fourth lactation. The percentage of muscle polypeptide in the isoenzymes showed a progressive, constant increase from 78.17% in virgin mice to 82.57% in mice after the first lactation, 86.05% after the second, 86.08% after the



d, and 87.14% in mice with spontaneous Bittner's tumor at the fourth lactation. The muscle/heart polypeptide quotient increased accordingly from about 3.5 in virgin mice to nearly 9 in those with tumors. The findings show that the enzyme pattern acquires preneoplastic characteristics during the second lactation. (8 refs.)

**78-1606 Long-Term Effects of Neonatal Hormonal Treatments on Plasma Prolactin Levels in Male BALB/cfC3H and BALB/c Mice.** (Eng) Nagasawa, M. (Pharmacology Div., Natl. Cancer Center Res. Inst., Chuo-ku, Tokyo 104, Japan); Mori, T.; Yanai, R.; Nishimura, H. A.; Mills, K. T. *Cancer Res* 38(4): 942-945; 1978.

An investigation was made of plasma prolactin levels at various ages in female BALB/cfC3H/Crgl (mammary tumor virus-expressed) and BALB/cCrgl (mammary tumor virus-unexpressed) mice who received daily sc injections of 5 µg diethylstilbestrol (DES), 20 µg DES, 20 µg 17β-estradiol (E2), 20 µg testosterone (T), or 20 µg ovine prolactin (OPRL) for the first 5 days postnatally. In mice killed at 2, 7, and 15 mo of age, plasma prolactin levels in BALB/cCfC3H mice treated with DES, E2, or OPRL were comparable to those in controls at proestrus/estrus and usually significantly higher than control levels at metestrus/estrus. Prolactin levels in mice treated with T were usually significantly higher than those in the other treated groups and all controls. In BALB/c females at about 7 and 15 mo, DES-treated groups had findings similar to those in BALB/cfC3H mice. T treatment resulted in levels greater than those in controls at either of the above-mentioned stages. In both substrains, mice given steroid hormones or DES had corpora lutea at all ages, but control mice and mice receiving OPRL showed corpora lutea. Mammary tumor responses to neonatal steroid or DES treatment may in part be ascribed to continuous estrogen stimulation of prolactin secretion. (22 refs)

**78-1607 Quantitative Comparison of Milk-Released C3H and RIII Mammary Tumor Viruses in Infected BALB/c Hosts.** (Eng) Bistocchi, M. (Istituto di Anatomia e Istologia Patologica, Scuola Medica, Via Roma 57, 50100 Pisa, Italy); Nuti, M.; Squartini, F. *Tumori* 63(6): 535-542; 1977.

The production of mammary tumor virus (MTV) was quantitated during the first three lactation periods of BALB/cfRIII and BALB/cfC3H mice. The females were grouped according to age at birth, age at first delivery, and litter size; milk samples were collected on days 5-8 using a breast pump. In every female, MTV release increased with each successive lactation; large individual variation within each strain was also apparent. Furthermore, the amount of MTV released by BALB/cfRIII mice was approx double that of BALB/cfC3H mice

at each lactation. Since the bioactivity of RIII MTV is less than that of C3H, this difference is inherent to the type of MTV. (23 refs)

**78-1608 The Distribution of Mouse Mammary Tumor Virus (MMTV) Antigens in BALB/cf C3H Mammary Tissues (Meeting Abstract).** (Eng) St. George, J. A. (Univ. California, Davis, CA, 95616); Cardiff, R. D.; Young, L. J.; Faulkin, L. J. *Proc Am Assoc Cancer Res* 19: 51; 1978. (no refs)

**78-1609 Infectivity of Various Mammary Tumor Viruses in F1 Hybrid Mice (Meeting Abstract).** (Eng) Moore, D. H. (Hahnemann Medical Coll., Philadelphia, PA, 19102). *Proc Am Assoc Cancer Res* 19: 39; 1978. (no refs)

**78-1610 Loss of Differentiative Potential of Salivary Epithelium Neoplastically Transformed Prior to Cytodifferentiation (Meeting Abstract).** (Eng) Dawe, C. J. (NCI, Bethesda, MD, 20014); Williams, J. E.; Morgan, W. D.; Summerour, J. P. *Proc Am Assoc Cancer Res* 19: 86; 1978. (no refs)

**78-1611 PUVA Enhances the Frequency of Viral Transformation (Meeting Abstract).** (Eng) Morhenn, V. B. (Dept. Dermatology, Stanford Univ. Sch. Medicine, Stanford, CA); Kaye, J.; Farber, E. M. *Clin Res* 26(2): 209A; 1978. (no refs)

**78-1612 Transcription of a Defective Polyoma Virus Genome.** (Eng) Condit, R. (Health Sciences Center, State Univ. New York, Stony Brook, NY, 11594); Cowie, A.; Kamen, R.; Fried, M. *Proc Natl Acad Sci USA* 75(1): 69-73; 1978.

The in vitro transcription of wild-type polyoma virus (PV) DNA was compared with that of the DNA of a PV deletion mutant, D-50. The circular genome of the latter consists of tandemly repeated copies of the DNA sequence between 67 and 84 units on the wild-type polyoma virus DNA map. Thus, each repeated copy contains the origin of viral DNA replication, located at about 71 map units. Viral RNA was synthesized in vitro using viral transcription complexes extracted late (30 hr) after infection from mouse cells coinfecting with D-50 and helper wild-type virus. Both wild-type and D-50 DNA molecules were active as templates for in vitro transcription. Approx 84% of the RNA transcribed in vitro from wild-type DNA was complementary to the late (L)



DNA strand. By contrast, at least 90% of the RNA transcribed from D-50 DNA molecules was complementary to the early (E) DNA strand. After normalization of the data to account for the observed molar ratio of D-50 DNA repeated sequences to unit length wild-type DNA, the calculated transcription of the E DNA strand of each D-50 repeated unit is 1.4 times as efficient as transcription of the wild-type E DNA strand. Transcription of the D-50 L DNA strand, however, is only 0.03 times as efficient as transcription of the wild-type L DNA strand. (36 refs)

- 78-1613 Polyoma Virus Complementary RNA Directs the In Vitro Synthesis of Capsid Proteins VP1 and VP2.** (Eng) Mangel, W. F. (Dept. Biochemistry, Univ. Illinois, Urbana, IL, 61801); Hewick, R. M.; Bayley, S. T.; Wheeler, T.; Harvey, R.; Waterfield, M. D.; Smith, A. E. *J Virol* 25(2): 570-578; 1978.

RNA complementary to large-plaque polyoma strain A2 DNA was synthesized and translated in vitro in a cell-free system. The polypeptides that were synthesized comigrated with the polyoma capsid proteins VP1 (45,000 daltons) and VP2 (34,000 daltons). Study of the in vitro- and virion-derived VP1 and VP2 revealed them to be identical. It is concluded that the proteins VP1, VP2, and VP3 are entirely virus-coded. (39 refs)

- 78-1614 An Epithelial Cell Line with Chronic Polyoma Infection Established from a Spontaneous Mouse Pancreatic Adenocarcinoma.** (Eng) Leiter, E. H. (Jackson Lab., Bar Harbor, ME, 04609); Malinoski, F. J.; Eppig, J. J. *Cancer Res* 38(4): 969-977; 1978.

The establishment of an epithelial cell line (LTPA) from a pancreatic adenocarcinoma in a 12-mo-old LT/Sv mouse is reported. The cell line was aneuploid, exhibited a rapid growth rate, failed to show density-dependent inhibition of growth, and grew in defined medium. A C-type oncornavirus was isolated from the culture medium, and electron microscopy revealed the presence of intracisternal A-type particles. The cells also carried a persistent polyoma infection that produced only low levels of cytopathic effects. Mycoplasma contamination was detected but was not classified serologically. Injection of LTPA cells into adult LT or (LT x C57BL/6J)F<sub>1</sub> mice failed to produce tumors, but when  $2.4 \times 10^6$  cells were injected id into irradiated female Swiss nu/nu mice, ductular structures were formed that were destroyed by inflammatory reactions within 3 wk. Three male nu/nu mice were given  $1.68 \times 10^6$  cells ip, and one of these had a reticulum cell sarcoma of the pancreas upon autopsy 1 mo later. (23 refs)

- 78-1615 Biological Activities of Solubilized Surface Antigens of Embryonic and Polyoma-Virus-**

**transformed Cells.** (Eng) Kitahara, Y. (Unit 119, INSERM 27 Bd. Le Roure, 13009 Marseille, France); Barra, Y.; Meyer, G. *Br J Cancer* 37(1): 41-47; 1978.

Virus-induced antigens were studied in the polyoma virus mouse system using the technique of KCl solubilization of the membrane components. Both tumor-specific transplantation antigen (TSTA), demonstrated by homograft rejection and surface (S) antigen, detected by inhibition of immunofluorescence on polyoma virus-transformed 3T3b mouse cells, were identified in the soluble extracts. The crude soluble extracts were partially purified by successive precipitation with  $(\text{NH}_4)_2\text{SO}_4$ . In the polyoma virus-transformed cells, TSTA and a part of the S-antigen activity were found in the same fraction [60%  $(\text{NH}_4)_2\text{SO}_4$  saturation], but the greater part of S antigen was precipitated at 80% saturation. Chromatography on Biogel A indicated that two components possess S-antigen activity: one specific to transformed cells and the other common to both transformed and embryonic cells. These results suggest that S antigen may be composed of TSTA and the component common to the embryonic antigen, which may be an oncofetal antigen. The balance between these two antigens during tumor evolution may determine the response of the host defense mechanisms. (15 refs)

- 78-1616 Similarity of Nucleotide Sequences Around the Origin of DNA Replication in Mouse Polyoma Virus and Simian Virus 40.** (Eng) Soeda, E. (Natl. Inst. Genetics, Mishima 411, Japan); Kimura, G.; Miura, K. *Proc Natl Acad Sci USA* 75(1): 162-166; 1978.

The nucleotide sequence at the origin of polyoma virus DNA replication was determined by using DNA polymerase to label the 3' terminus of the *Hap II-5/Alu I-1* DNA fragment with  $^{32}\text{P}$ . The results coincided with those obtained with  $^{32}\text{P}$  labeling, using polynucleotide kinase, of the 5' terminus of the *Hap II-5/Hha I-1* DNA fragment, *Hap II-5/Alu I-1*. A symmetrical (A+T)-rich region containing a five-A stretch (or a five-T stretch) was flanked by two small regions with a rotational axis of symmetry. Of the 82 nucleotides in the polyoma virus DNA segment sequence, 58 were identical with those in the corresponding region of simian virus 40 DNA. Since recombination occurs most frequently in this region, the polyoma virus and simian virus 40 could be descended from a common ancestor. (30 refs)

- 78-1617 Infection of Mouse Preimplantation Embryos with Simian Virus 40 and Polyoma Virus.** (Eng) Abramczuk, J. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104); Vorbrodt, A.; Solter, D.; Koprowski, H. *Proc Natl Acad Sci USA* 75(2): 999-1003; 1978.

Mouse two-cell embryos, morulae, and blastocysts were killed when infected in vitro with simian virus 40 (SV40) a



multiplicities of infection. Polyoma (Py) virus was not virious for preimplantation embryos, even at a very high multiplicity of infection; however, the outgrowths of Py-embryonated blastocysts disintegrated after several days of culture. Indirect immunofluorescence tests revealed the presence of SV40 T and V antigens and Py virus V antigen in the nuclei of trophoblastic cells. Virus-specific antigens were not detected in the nuclei of cells forming inner cell masses of blastocysts or in inner cell mass-derived cells in blastocyst outgrowths. The appearance of SV40 T and V antigens in the nuclei was inhibited by  $\alpha$ -amanitin, an RNA polymerase II inhibitor. The amount of infectious virus recovered from cultures of morulae or blastocysts subsequent to SV40 declined initially but later increased. These results indicate that some early mouse embryos are permissive for the expression of early and late functions of the SV40 genome and that susceptibility to infection with Py virus and/or permissiveness for expression of Py virus late functions develops gradually between the two-cell and blastocyst stages. Electron micrographs showed the presence of specific complexes of membranes and virions in the cytoplasm of trophoblastic cells. Single viral particles were present in the nuclei and also in mitochondria. (18 refs)

518 **Transformation of BALB/c-3T3 Cells by *tsA* Mutants of Simian Virus 40: Temperature Sensitivity of the Transformed Phenotype and Retransformation with Wild-Type Virus.** (Eng) Brockman, W. W. (Dept. Microbiology, Univ. Michigan Medical Sch., Ann Arbor, MI, 48106). *J Virol* 25(3): 860-870; 1978.

Function of the *A* gene of simian virus 40 (SV40) in transforming BALB/c-3T3 cells was investigated by infecting 19 lines of cells at the permissive temperature with wild-type SV40 strain 776 and with six *tsA* mutants whose mutation maps at different positions in the early region of the genome. Of 16 *tsA* transformants, 15 were temperature-sensitive for the ability to overgrow a monolayer of normal cells, while 3/3 wild-type transformants were not. This pattern of temperature sensitivity of the transformed phenotype was also observed when selected clones were assessed for the ability to grow in soft agar and in medium containing low concentrations of serum. The temperature resistance of the exceptional *tsA* transformant (transformed by *A7*) could be attributed neither to the location of the mutation site in the transforming virus nor to transformation by a revertant virus. However, this transformant contained a higher intracellular concentration of SV40 T antigen than another *A7* transformed temperature-sensitive line. A *tsA* transformant displaying the untransformed phenotype at the nonpermissive temperature was susceptible to retransformation by wild-type virus at this temperature, demonstrating that the temperature sensitivity of the *tsA* transformants is due to the viral gene and not to a cellular defect. Thus, continuous expression of the SV40A gene product is required to maintain the transformed phenotype in BALB/c-3T3 cells. (44 refs)

78-1619 **Ligation of Nicked SV40 DNA in a Polyethylene Glycol-condensed State as a Test for Net Coiling (Letter to Editor).** (Eng) Griffith, J. D. (Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514). *Biopolymers* 17(1): 237-241; 1978.

Simian virus 40 (SV40) form II was mixed with high concentrations of polyethylene glycol (PEG) and, after its removal from the PEG solution, examined for the presence of superhelical turns in order to determine the net coiling that occurred in the PEG-condensed state. SV40 form I DNA was isolated from CV-1 cells and converted to form II with DNase in ethidium bromide. Following ligation and purification, DNA molecules were examined by electron microscopy. In the presence of ethidium bromide, molecules that had become covalently closed appeared as tightly twisted rods; closing efficiency ranged from 35%-60%. Examination without ethidium bromide dye revealed no tightly twisted rods, but 35%-60% of the molecules showed one to five superhelical twists. Agarose gel electrophoresis revealed that ligated SV40 DNA had prominent bands at the position of relaxed SV40 DNA and four to five bands migrating ahead of that; no highly twisted molecules were observed. The four to five bands migrating ahead of the relaxed DNA appeared to correspond in number and intensity to the molecules with superhelical twists observed electron microscopically. These findings suggest that a condensation occurred in the DNA without the addition of any net twisting of the DNA molecule beyond that imposed by random fluctuations of the DNA structure. (13 refs)

78-1620 **Induction of Sister Chromatid Exchanges by Transformation with Simian Virus 40.** (Eng) Nichols, W. W. (Inst. Medical Res., Camden, NJ, 08103); Bradt, C. I.; Toji, L. H.; Godley, M.; Segawa, M. *Cancer Res* 38(4): 960-964; 1978.

The frequency of sister chromatid exchanges (SCE) was studied in four human diploid fibroblast cultures before and after the addition of simian virus 40 (SV40). Culture GM 302 was derived from normal skin, HEL 76 from normal lung, AG 1979 from a patient with sporadic retinoblastoma, and GM 1142 from a patient with retinoblastoma associated with a deletion of chromosome 13. The SCE frequency was nearly the same in uninfected controls and in infected cultures before they became tumor (T)-antigen positive. When the cells exhibited T antigen, the SCE frequency increased over a wide range. With multiplicities of virus to cell between 6 and 18, the cells became T-antigen positive between passages 8 and 10. With a multiplicity of 100 plaque-forming units/cell, the cells were positive by the first passage when SV40 antiserum was not used and by the fourth to sixth passages when antiserum was present. When the cells became T-antigen positive, changes in chromosome number and structure were observed. Cells with induced chromosome abnormalities without increased SCE and vice versa suggest that



the two phenomena may have different viral mechanisms. (22 refs)

- 78-1621 Organization and Expression of Early Genes of Simian Virus 40.** (Eng) Crawford, L. V. (Dept. Biochemistry, Stanford Univ. Medical Center, Stanford, CA, 94305); Cole, C. N.; Smith, A. E.; Paucha, E.; Tegtmeyer, P.; Rundell, K.; Berg, P. *Proc Natl Acad Sci USA* 75(1): 117-121; 1978.

The early region of simian virus 40 (SV40) codes for at least two immunologically related polypeptides: large T and small t, with mol wt of 90,000-100,000 and 15,000-20,000, respectively. Because small t shares methionine-containing tryptic peptides with large T, the two polypeptides are probably coded, in part, by a common nucleotide sequence. To locate the coding sequences, the production of these proteins was examined after infection of CV-1 cells with wild-type and deletion mutants of SV40. A deletion at the distal portion of the early region altered the structure of T but not that of t; however, deletions within the region between map coordinates 0.59 and 0.55 resulted in an alteration or absence of t and a normal T. These findings are explained by a model that proposes the existence of two early messenger RNA's (mRNA), one coding for T and the other for t. Both mRNA's span virtually the entire early region, but the mRNA coding for T lacks the nucleotide sequence between map coordinates 0.59 and 0.54. It is suggested that t is translated from the larger of the two mRNA's, beginning at or near its 5' end and terminating at a termination codon at about map coordinate 0.54. T, on the other hand, is translated from the shorter mRNA, beginning at the same initiator codon; because of the deletion of the terminator codon at 0.54, its translation proceeds to the terminator codon at or near map position 0.18. (31 refs)

- 78-1622 Exogenous DNA Transcription in Cells with Their Native DNA Inhibited. II. Informosomes Produced under the Effect of Exogenous DNA.** (Eng) Die, R. (Dept. Biology and Biochemistry Cancer, Instituto Nacional de Oncologia, Ciudad Universitaria, Madrid-3, Spain); Valladares, Y.; Alvarez, Y.; Alvarez-Noves, J. *Rev Esp Oncol* 24(1): 31-41; 1977.

The existence of specific genetic information, detected at the level of informosome (cytoplasmic messenger RNA + protein particle) production was investigated in TC-simian virus 40 (SV40) cells (SV40-induced hamster tumor established in vitro) and in EAC cells (Ehrlich-Lettre ascites cancer). Free informosomes isolated from TC-SV40 cells gave peaks at 1.49 and 1.32 g/cm<sup>3</sup> when analyzed on a CsCl gradient, but those from EAC cells gave peaks at 1.49, 1.39, and 1.32 g/cm<sup>3</sup>. Free informosomes were not detected in TC-SV40 cells in which the endogenous DNA had been treated with 5-bromodeoxyuridine followed by UV exposure to block transcription. However, when these blocked TC-SV40 cells were

inoculated with exogenous EAC DNA, informosomes were again detected at densities of 1.45 and 1.40 g/cm<sup>3</sup>, which correspond to the densities of the informosomes isolated from EAC cells rather than those of the informosomes isolated from untreated TC-SV40 cells. These results indicate that exogenous DNA isolated from cancer cells is able to develop specific transcriptional activity when it is introduced into host cell in which the endogenous transcription has been inhibited. (30 refs)

- 78-1623 Serum Activity Inhibiting Specific Simian Virus 40-induced Transplantation Resistance and Correlation with Primary SV40 Tumors Appearance in Hamsters.** (Eng) Volpe, E. A. (Lab. Tumor Immunology, Cancer Res. Center, Kashirskoye shosse 6, Moscow 115 478, USSR) *Experientia* 15(1): 113-116; 1978.

Serum activity inhibiting specific simian virus 40 (SV40) induced transplantation resistance (ITR) and its correlation with the appearance of primary SV40 tumors were studied in Syrian hamsters. Serum samples were obtained during different periods of primary SV40-induced carcinogenesis. SV40 tumor cells were pretreated with these serum samples in vivo and subsequently used to challenge immune (SV40-inoculated) and normal adult hamsters. ITR serum activity was found in 14/21 hamster sera obtained during the late period of primary SV40 carcinogenesis (60 days after neonatal virus infection). No ITR activity was observed in the sera of the same hamsters after tumor appearance and during tumor growth. ITR activity rapidly disappeared from sera of hamsters neonatally infected with SV40 after their successful immunization with the same virus during the latent period. There appears to be a correlation between the presence of ITR serum factor during the latent period and the subsequent primary SV40 tumor appearance in hamsters. The ITR serum factor detected in these in vivo studies differs from the serum lymphocyte blocking factor detected by others in in vitro assays. The role of ITR serum factor in vivo is not known, but it may reflect the process of primary carcinogenesis and may be favorable for tumor development. (23 refs)

- 78-1624 Suppression of Endogenous Isorenin by the Oncogenic Virus SV40 after Injection of 3T3 Cells.** (Eng) Fischer, H. (Inst. Virus Res., German Cancer Research Center, 6900 Heidelberg, W. Germany); Schelling, P.; Garren, D. *IARC Med Sci [Cancer]* 6(1): 11; 1978.

Isorenin concentrations in 3T3 and simian virus 40 (SV40 strain Rh 911)-transformed SV3T3 cells were examined. One to 2 days after SV40 infection, the isorenin concentration decreased, indicating that the virus was suppressing isorenin synthesis. After multiple passages, all cells became T-antigen positive, and they had reduced isorenin levels. No suppression of isorenin synthesis was noted in uninfected cells. (refs)



- 625 **Mobility of Cells from Solid Tumors.** (Eng) Gershman, H. (Dept. Biochemistry, Case Western Reserve Univ., Cleveland, OH, 44106); Katzin, W.; R. T. *Int J Cancer* 21(3): 309-316; 1978.

mobility of cells from two established cell lines of ham-  
origin, NIL B and its simian virus 40 transformant SV-  
was studied in cellular aggregates to determine if selec-  
or in vivo growth is accompanied by an enhanced ability  
ove about in vitro. Sc injection of  $5 \times 10^6$  NIL B or  
NIL cells into Syrian hamsters resulted in 100% tumor  
ation with SV-NIL and 93% tumor formation with NIL  
l tumors were locally invasive. Cells from five different  
rs of NIL B origin were grown in tissue culture, and  
mobility in cellular aggregates was also studied. The  
lities of the tumor-derived cells were similar to each oth-  
d to those of the SV-NIL cells, but slightly higher than  
of the NIL B cells. The plating efficiency, saturation  
ty, and doubling time of NIL B, SV-NIL, and the tu-  
derived cells were also determined. No consistent pat-  
of saturation density or doubling time was observed in  
umor-derived cells with respect to each other or to the  
lished lines; however, the plating efficiencies of the tu-  
derived cells were all considerably lower than those of  
B and SV-NIL cells. It was concluded that the ability  
vide and form tumors in vivo was accompanied by a  
est increase in in vitro cell mobility. (23 refs)

- 626 **Uridine Transport Properties of Mammalian Cell Membranes Are Not Directly Involved Growth Control or Oncogenesis.** (Eng) Koren, R. (Inst. Sciences, Biophysics Section, Hebrew Univ., Jerusalem, I); Shohami, E.; Bibi, O.; Stein, W. D. *FEBS Lett* 86(1): 3; 1978.

ine transport was investigated in 3T3 mouse fibroblasts  
simian virus 40 (SV40)-transformed 3T3 cells. The Km  
ormal and SV40-transformed cells was the same whether  
ystem was activated by serum or not ( $10^{-4}$  M). The max  
port velocity was statistically greater for transformed  
The results, and those in the literature, suggest that the  
ne transport system in different cells is essentially similar  
that it is not the transport of uridine that is responsible  
the changes in uridine uptake that occur when cells are  
ulated to grow or are transformed. (14 refs)

- 627 **Biosynthesis of Proteins in LLC-MK<sub>2</sub> Cells Infected with SV40(MK<sub>2</sub>) Virus.** (Spa) Valladares, Departamento de Biología y Bioquímica del Cáncer, Instituto Nacional de Oncología, Ciudad Universitaria, Madrid-3, Spain); Alvarez-Rodriguez, Y.; Iturriza, R. G. *Rev Oncol* 24(1): 7-14; 1977.

ein biosynthesis was studied in the LLC-MK<sub>2</sub> continuous

cell line (from a *Macaca mulatta* kidney) infected with simian virus 40 strain MK<sub>2</sub> [(SV40)MK<sub>2</sub>: titer,  $6.25 \times 10^4$  median tissue culture infective dose]. Infection resulted in the production of a small amount of virus and a slight cytopathogenic effect, followed by inhibition of virus production and recovery of the growth capacity of the colony. Study of the ribosomes revealed an increased number of monomers and an increase in overall ribosome formation during the first phase of infection. The number of polyribosomes with two and four units and the number of incomplete dimers were increased after 2 hr. An increase in polyribosomes with four and five units, a complex with eight or more units, and the formation of abnormal polyribosomes were seen after 24 hr. The ribosomes were completely disorganized at 48 hr, but by 4 days, they had become reorganized and cell proliferation was back to normal. The results indicate that ribosomal activity is first used for the simultaneous synthesis of virus particles and of a factor that prevents reinfection. This process of protein biosynthesis is totally different from that observed in lytic and abortive infections. (4 refs.)

- 78-1628 **Endogenous New World Primate Type C Viruses Isolated from Owl Monkey (*Aotus tri-virgatus*) Kidney Cell Line.** (Eng) Todaro, G. J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Sherr, C. J.; Sen, A.; King, N.; Daniel, M. D.; Fleckenstein, B. *Proc Natl Acad Sci USA* 75(2): 1004-1008; 1978.

A C-type virus (OMC-1) detected in a culture of owl monkey kidney cells resembled typical C-type viruses morphologically, but it was slightly larger than previously characterized C-type mammalian viruses. OMC-1 replicated only in bat lung cells and cat embryo fibroblasts. The virions banded at a density of 1.16 g/ml in isopycnic sucrose density gradients, and they contained reverse transcriptase and a 60S-65S RNA genome composed of approx 32S subunits. The reverse transcriptase was immunologically and biochemically distinct from the polymerases of other retroviruses. Competitive radioimmunoassay demonstrated that OMC-1 does not share interspecies antigenic determinants with other C-type viruses. Nucleic acid hybridization experiments using labeled viral genomic RNA or proviral complementary DNA transcripts to normal cellular DNA of different species showed that OMC-1 is an endogenous virus with multiple viro gene copies (20-50/haploid genome) present in normal owl monkey cells and that it is distinct from previously isolated C- and D-type viruses. Sequences related to the OMC-1 genome can be detected in other New World monkeys. Thus, both the Old World primates and the New World monkeys contain endogenous C-type viral genes that appear to have been transmitted in the primate germ line. (39 refs)

- 78-1629 **Isolation and Tissue Distribution of Type-C Virus and Viral Components from a Gibbon Ape (*Hylobates lar*) with Lymphocytic Leukemia.** (Eng) Gallo, R.



C. (Lab. of Tumor Cell Biology, NCI, NHI, Bethesda, MD, 20014); Gallagher, R. E.; Wong-Staal, F.; Aoki, T.; Markham, P. D.; Schetter, H.; Ruscetti, F.; Valerio, M.; Walling, M. J.; O'Keefe, R. T.; Saxinger, W. C.; Smith, R. G.; Gillespie, D. H.; Reitz, M. S. *Virology* 84(2): 359-373; 1978.

Tissues obtained at necropsy from a 7-yr-old male gibbon ape (*Hylobates lar*) with malignant lymphoma and leukemia were examined by light and electron microscopy. The tissues were infiltrated with tumor cells of lymphoblast morphology, the most extensively involved being the kidneys, ureters, liver, lymph nodes, heart, salivary glands, and mesentery. C-type virus particles were abundant in the plasma and were seen in all tissues tested. Tissue extracts contained viral p30, reverse transcriptase, viral RNA, and proviral DNA in amounts that correlated with the degree of leukemic cell infiltration. Viral markers were particularly abundant in tissue from the oral cavity, suggesting that the oral route is a likely mode of virus transmission. Proviral DNA was found in all tissues except muscle and brain. Replicating virus was transmitted to heterologous cells in tissue culture from many tissues, including muscle and brain. The virus, designated gibbon ape leukemia virus-H (GaLV-H), was classified as a member of GaLV-simian sarcoma virus (GaLV-SiSV) group by comparative tests of the antigenic relatedness of p30 and reverse transcriptase and by nucleotide sequence homology of the RNA from this virus and from other members of the group. These results establish the GaLV-SiSV virus group as a major etiological factor in the development of leukemia and lymphoma in captive *Hylobates lar* and argue against a large tissue reservoir of virus outside the tumor cells. (40 refs)

**78-1630 Characteristics of Primate C-Type Oncor-naviruses.** (Rus) Voevodin, A. F. (Inst. Experimental Pathology and Therapy, Sukhumi, USSR); Lapin, B. A.; Yakovleva, L. A.; Diyachenko, A. G.; Kakubava, V. V.; Lovenetsky, A. N.; Agrba, V. Z. *Vestn Akad Med Nauk SSSR* (10): 77-78; 1977.

Some properties of BILN virus, which was isolated from the lymph node of a baboon with hemoblastosis, are described. Immunologically, the chief structural protein of virus BILN (p30) was almost indistinguishable from analogous proteins of other C-type oncornaviruses. Interspecies antigenic determinants characteristic for p30 were detected in 7/14 spleen extracts from baboons with hemoblastosis. Quantitative assay of the p30 content in various tissues of baboons with hemoblastosis showed a correlation between p30 content and degree of lymphoid proliferation. (6 refs.)

**78-1631 Infectivity Studies with v-L104, a Primate On-cornavirus Isolated from Human Tumor Cells (Meeting Abstract).** (Eng) Gabelman, N. (Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029);

Robinson, A.; Ong, S.; Waxman, S. *Proc Am Assoc Cancer Res* 19: 7; 1978. (no refs)

**78-1632 Oncornavirus Lytic Activity in the Serum of Gibbon Apes.** (Eng) Gallagher, R. E. (Lab. Tumor Cell Biology, NCI, NIH, U.S. Dept. Health, Education and Welfare, Bethesda, MD 20014); Schrecker, A. W.; Walter, C. A.; Gallo, R. C. *J Natl Cancer Inst* 60(3): 677-682; 1978.

A heat-sensitive mammalian oncornavirus lytic activity (SOLA) was demonstrated in sera from normal gibbon apes. SOLA levels were similar in animals with and without antibodies to gibbon ape leukemia virus. A leukemic-viremic gibbon had little or no SOLA and no free antibodies to leukemia virus. The possibility that SOLA may limit virus replication and dissemination is discussed. (19 refs.)

**78-1633 Molecular Mechanisms Involved in the Differential Expression of gag Gene Products by Clonal Isolates of a Primate Sarcoma Virus.** (Eng) Robbins, K. C. (Hazleton Lab., Vienna, VA, 22180); Okabe, H.; Tro-nick, S. R.; Gilden, R. V.; Aaronson, S. A. *J Virol* 25(2): 471-478; 1978.

The molecular mechanisms responsible for the differential expression of Woolly monkey helper virus (WLV) gag gene products by clonal variants of Woolly monkey sarcoma virus (WSV) were investigated. Three WSV RNA genomes had sedimentation coefficients consistent with the differences demonstrated in their allotments of helper viral sequences. The WSV variant (WSV clone 9) that expressed no detectable gag gene products contained the largest amount of helper viral information. Moreover, there was no additive hybridization of the WLV complementary DNA probe by the RNA of this WSV clone and that of a WSV clone coding for several gag gene products. These results suggest that the lack of expression of gag gene products by WSV clone 9 is not due to a major deletion of helper viral gag gene sequences. Similar WLV specific RNA levels were demonstrated in cells nonproductively transformed by each WSV clone, indicating that the ability to express gag gene proteins was not related to the magnitude of viral RNA transcription. The results are consistent with a mechanism by which small deletions or point mutations in the genomes of some WSV variants result in premature termination of translation or synthesis of immunologically nonreactive gag gene proteins. The potential effects of evolutionary selective pressures on helper viral genetic information in mammalian transforming viruses are discussed. (38 refs)

**78-1634 Characteristics of Hamster Cells Transformed by the Combined Action of Chemical and Virus**



Hatch, G. G. (BioLabs, Inc., 2910 MacArthur Blvd., Northbrook, IL 60062); Balwierz, P. J.; Casto, B. C.; DiPaola, A. *Int J Cancer* 21(1): 121-127; 1978.

Characteristics of primary hamster cells transformed by adenovirus SA7 or a chemical carcinogen alone were compared with those of cells transformed by combined viral and chemical action. All transformed cells resulting from treatment with virus or chemical alone [3-methylcholanthrene (MCA), benzo(a)pyrene (BP), dibenz(a,h)anthracene, 7,12-dimethylbenz(a)anthracene (DMBA), 4-aminobiphenyl, methylnitrosamine, methylazoxymethanol acetate] retained complement-fixing SA7 T antigen, but the amount of antigen could not be correlated with the type of chemical used for pretreatment. None of the cells transformed by SA7 or MCA alone contained hamster tumor antigens. All cell lines transformed by virus or chemical alone or in combination formed colonies in agar. Although quantitative differences in cloning efficiency were noted, they could not be correlated with the chemical used. Control secondary hamster cell cultures did not form colonies. Cells transformed by MCA only grew up to 50 times greater cloning efficiency than cells transformed by virus only; their ability to clone was directly related to the passage level. When MCA-transformed cells were subsequently transformed by SA7, cloning efficiency most closely resembled that of virally transformed cells. The tumorigenicity of virally transformed cells was similar to that of virally transformed cells. However, four transformed lines pretreated with MCA, BP, or DMBA increased the tumor incidence or shortened the latent period compared with SA7 transformation alone. MCA-transformed cells produced tumors in 30/30 weanling hamsters, MCA-SA7 cells in 18/30, and cells in 24/73. (20 refs.)

635 **Fragmentation of Simian Adenovirus Type 7 by Specific Endonucleases R.SaI and R.BamI.** (Eng) Naroditsky, B. S. (D. I. Ivanovsky Inst. Virology, Moscow, USSR); Zavizion, B. A.; Karamov, E. V.; Chaplygina, I.; Dreizin, R. S.; Zolotarskaya, E. E.; Tikhonenko, V. *Vopr Virusol* (1): 36-42; 1978.

Effect of restriction endonucleases R.EcoRI, R.BamI, R.SaI on the genome of simian adenovirus type 7 (SA-7) was studied. R.EcoRI separated the SA-7 DNA into two fragments with mol wts of 12 and 10 x 10<sup>6</sup>. Treatment with R.BamI produced seven fragments, treatment with R.SaI six. Recognition site for R.EcoRI was located in the C fragment of R.Bam and in B fragment of R.SaI. It is suggested that the oncogenic properties of SA-7 are associated with the recognition sites for R.BamI and R.SaI. (7 refs)

636 **Attenuated Herpesvirus Saimiri (HVS): Protection of Marmosets Against Challenge with On-**

cogenic HVS (Meeting Abstract). (Eng) Falk, L. (Dept. Microbiology, Rush-Presbyterian-St. Luke's, Chicago, IL, 60612); Wright, J.; Wolfe, L. *Proc Am Assoc Cancer Res* 19: 189; 1978. (no refs)

78-1637 **Properties of Lymphoid Cells Transformed by Epstein-Barr Virus (EBV) or EBV-like Simian Viruses (Meeting Abstract).** (Eng) Rabin, H. (Frederick Cancer Res. Center, Viral Oncology Program, NCI, P.O. Box B, Frederick, MD, 21501); Neubauer, R. H.; Hopkins, R. F. *Proc Am Assoc Cancer Res* 19: 11; 1978. (no refs)

78-1638 **Expression of Epstein Barr Nuclear Antigen (EBNA) and Malignant Phenotype in Somatic Cell Hybrids Between Mouse Cells and Human Nasopharyngeal Carcinoma Cells (Meeting Abstract).** (Eng) Steplewski, Z. (Wistar Inst., Philadelphia, PA, 19104). *Proc Am Assoc Cancer Res* 19: 29; 1978. (no refs)

78-1639 **Large-Scale Production and Concentration of Infectious Epstein-Barr Virus.** (Eng) Klein, F. (Frederick Cancer Res. Center, Frederick, MD, 21501); Rosensteel, J. F.; Hummer, R. M.; Hillman, E. A.; Riggs, C. W.; Charmella, L. J. *Appl Environ Microbiol* 35(1): 172-178; 1978.

A method is given for the production of large amounts of infectious Epstein-Barr virus (EBV) from suspension cultures of the P3HR-1 producer line. Virus from the culture fluid was concentrated by continuous-flow pelletization or continuous flow with banding in sucrose. EBV prepared by the former yielded 1.7 x 10<sup>6</sup> infectious units/ml (100x concentration) and <3.4 x 10<sup>7</sup> EBV particles/ml (1,000x concentration), but EBV prepared by banding yielded 4.6 x 10<sup>7</sup> infectious units/ml (100x concentration) and 1.3 x 10<sup>8</sup> EBV particles/ml (1,000x concentration). The majority of the virus particles observed were 'empty' membrane-associated particles. In no case did the degree of correlation between infectivity and virus particle count attain statistical significance. This lack of correlation could be attributed to the volume of the culture fluid being processed, the concentration factor, and the presence of cellular debris. (19 refs)

78-1640 **Induction of EBNA Precedes the First Cellular S-Phase After EBV-Infection of Human Lymphocytes.** (Eng) Einhorn, L. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Ernberg, I. *Int J Cancer* 21(2): 157-160; 1978.

Immunofluorescence and autoradiography were used to



study the appearance of Epstein-Barr nuclear antigen (EBNA) and DNA synthesis in cord blood lymphocytes after they were infected with Epstein-Barr virus (EBV) derived from B95-8 cells. One milliliter of the virus-containing B95-8 supernatant was incubated with the lymphocytes for 1 hr. EBNA appeared between 12 and 25 hr after addition of the virus and remained at a plateau until DNA synthesis was detected (approx 20 hr after EBNA induction). This indicates that EBNA induction precedes the first cellular S phase and suggests that the cells have not yet entered the division cycle when EBNA appears. Little, if any, of the total DNA synthesis induced at this stage can be attributed to EBV-mediated immunologic stimulation, as indicated by the lack of DNA synthesis in EBNA-negative cells. (15 refs)

- 78-1641 Appearance of Early and Late Components of Epstein-Barr Virus-associated Membrane Antigen in Daudi Cells Superinfected with P3HR-1 Virus.** (Eng) Sairenji, T. (Dept. Microbiology, Kumamoto Univ. Medical Sch., Kumamoto, 860, Japan); Hinuma, Y.; Sekizawa, T.; Yoshida, M. *J Gen Virol* 38(1): 111-120; 1977.

The synthesis of membrane antigen (MA), virus capsid antigen (VCA) and early antigen (EA) in Daudi cells superinfected with the P3HR-1 strain of Epstein-Barr virus was investigated. Following infection, the cells were treated with trypsin to remove any MA-positive material from the cell surface. Increases in MA-, EA-, and VCA-positive cells were noted within the first 24 hr after injection, with the EA- and VCA-positive cells appearing about 3 hr after the MA-positive ones. Addition of 25  $\mu$ g/ml puromycin at the time of virus infection completely inhibited MA, EA and VCA synthesis, suggesting that the appearance of the antigens is due to de novo synthesis. Treatment of Daudi cells with 20  $\mu$ g/ml cytosine arabinoside (ara-C) inhibited MA and VCA synthesis, but not that of EA. Addition of 200  $\mu$ g/ml phosphonoacetate had no effect on EA synthesis. Differential absorption of Epstein-Barr virus antibody-positive human serum with the ara-C-treated or untreated infected cells detected two antigenically different components in MA: early (ara-C-insensitive) and late (ara-C-sensitive) MA. (27 refs.)

- 78-1642 Replication of Epstein-Barr Virus: Ultrastructural and Immunofluorescent Studies of P<sub>3</sub>HR1-superinfected Raji Cells.** (Eng) Seigneurin, J. M. (International Agency Res. Cancer, 69372 Lyon, France); Vuillaume, M.; Lenoir, G.; de-The, G. *J Virol* 24(3): 836-845; 1977.

Electron microscopy and immunofluorescence were used to study the different steps of the replication of the P<sub>3</sub>HR1 strain of Epstein-Barr virus in Raji cells. The virus entered the cells by fusion of the viral envelope with the plasma membrane, followed by disintegration of the capsid. In some cases, the EBV nucleocapsids migrated toward the nuclear membrane.

New virions were synthesized in the low-electron-density area of the nucleus; the time of their appearance ranged from 7 hr after a multiplicity of infection (MOI) of 800 particles/cell to 24 hr after an MOI of 100 particles/cell. A viral envelope was acquired by budding through the nuclear membrane or more often through membranes of the Golgi apparatus or cytoplasmic vacuoles. When immunofluorescence and electron microscope data were compared, a good correlation was found between the presence of early antigen (EA) and ultrastructurally altered cells, as well as between the presence of viral capsid antigen and virus-producing cells. The type of viral cycle depended on the MOI: at a low MOI ( $\leq 50$  particles/cell), a nonproducer cycle was induced with EA synthesis only; at a higher MOI (100 particles/cell), the transient production of a small amount of virions was observed; and at a high MOI ( $\geq 300$  particles/cell), a productive cycle was the rule. (24 refs)

- 78-1643 Epstein-Barr (EB) Virus Genome-containing EB Nuclear Antigen-negative B-Lymphocyte Populations in Blood in Acute Infectious Mononucleosis.** (Eng) Crawford, D. H. (Dept. Pathology, Medical School, Univ. Bristol, Bristol, England); Rickinson, A. B.; Finer, S.; Epstein, M. A. *J Gen Virol* 38(3): 449-460; 1978.

The type and size of cell infected by Epstein-Barr virus (EBV) in the blood of 32 patients (13-45 yr old) with acute infectious mononucleosis (IM) were identified, and the nature of infection was investigated. Virus-infected cells were restricted to the B-cell population, and only cultures of nonadherent cells had transformed foci. B-lymphocyte samples from eight IM patients were negative for EB nuclear antigen (EBNA) staining. The majority of virus-infected cells were found in fractions of normal-sized B cells, but these fractions were EBNA-negative. It is not certain whether these cells can persist in vivo, harboring the virus genome as a latent infection or whether they are in the early stages of the infectious cycle and are about to be destroyed by the immune response. If the latter is so, then the expression of EBV-associated lymphocyte-detected membrane antigen may precede that of EBNA. (49 refs)

- 78-1644 Excretion of Epstein-Barr Virus in Patients with Hodgkin's Disease (Meeting Abstract).** (Eng) Lange, B. (Children's Hosp. Philadelphia, Philadelphia, PA, 19104); Arbeter, A.; Hewetson, J.; Henle, W. *Proc Am Assoc Cancer Res* 19: 364; 1978. (no refs)

- 78-1645 Epstein-Barr Virus and Burkitt's Lymphoma (Letter to Editor).** (Eng) Wright, D. H. (Univ. of Southampton, Southampton SO9 4X4, England). *N Engl J Med* 298(9): 511; 1978.



ough it is established that Epstein-Barr virus (EBV) is etiologic agent in infectious mononucleosis, there is no definite proof that it plays a similar role in African Burkitt's lymphoma. The majority of African Burkitt's lymphoma develop from a clone of EBV-carrying B cells, but it yet to be proved that the virus acts either as an initiating promoting agent. (5 refs)

**78-1646 A Convenient Method of Establishing Permanent Lines of Xeroderma Pigmentosum Cells.** (Eng) Tohda, H. (Dept. Pharmacology, Res. Inst. for Tuberculosis and Cancer, Tohoku Univ., Sendai 980, Japan); Oikawa, A.; Katsuki, T.; Hinuma, Y.; Seiji, M. *Cancer Res* 38(3): 253-256; 1978.

A method was developed for establishing permanent lines of xeroderma pigmentosum (XP) cells by transforming peripheral lymphocytes with Epstein-Barr virus (EBV). Nine fibroblastoid cell lines were established using this technique from four XP patients, the parents of one XP patient, and three normal donors. These cell lines all proliferate as suspensions in Roswell Park Memorial Institute Medium 1640 supplemented with 20% fetal bovine serum. All nine cell lines carried EBV-associated nuclear antigen but did not release infectious virus. Transformation by EBV did not alter characteristics of XP, such as growth rate, chromosome number, UV sensitivity, and the defect in unscheduled DNA synthesis induced by UV, 4-nitroquinoline 1-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine. Since the procedure requires only a few ml of blood and the established cell lines are easy to grow in mass culture, the technique should be useful for biochemical studies on the mechanism of DNA repair. (16 refs.)

**78-1647 Malignant Melanoma after Herpes Zoster Infection.** (Ita) Depaoli, M. (II Divisione, Ospedale dermatologico S. Lazzaro, Turin, Italy); Buttafarro, G.; Pepino, E. *G Ital Dermatol* 112(11): 645-648; 1977.

A 55-yr-old woman who had a dormant pigmented nevus on her left palm for 30 yr developed a herpes zoster infection of the left brachial plexus, and, 1 mo later, the nevus was transformed into a malignant melanoma. Herpes zoster virus appears to be able to induce nevus cell mutation. (18 refs)

**78-1648 Humoral and Cellular Immunity to Herpesvirus Type 2 (HSV-2) Antigens in Exfoliated Cervical Epithelial Cells (Meeting Abstract).** (Eng) Bell, R. B. (Div. of Comparative Medicine, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205); Smith, C.; Aurelian, L. *Proc Am Assoc Cancer Res* 19: 193; 1978. (no refs)

**78-1649 In Vitro Transformation of Hamster Cells by a Human Cervical Tumor HSV-2 Isolate (Meeting Abstract).** (Eng) Jariwalla, R. J. (Div. Biophysics, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205). *Proc Am Assoc Cancer Res* 19: 165; 1978. (1 ref)

**78-1650 Controlled Inactivation of HSV-2 by BUdR + Light for Use in Transformation Studies (Meeting Abstract).** (Eng) Manak, M. M. (Div. Biophysics, Sch. Hygiene, Johns Hopkins Univ., Baltimore, MD, 21205). *Proc Am Assoc Cancer Res* 19: 64; 1978. (no refs)

**78-1651 Reduction of Intercellular Adhesiveness of Chick Heart Cells by Herpes Simplex Viruses 1 and 2.** (Eng) Batra, G. K. (Biosystems, Inc., P.O. Box 15146, Atlanta, GA, 30333); Nahmias, A. J.; DeHaan, R. L. *J Gen Virol* 38(3): 437-447; 1978.

The effects of herpes simplex virus type 1 (HSV-1, VR, strain) and HSV-2 (MS strain) infection on the adhesiveness of heart cells from 7-day-old chick embryos were determined. Cell monolayers were infected with HSV-1 or HSV-2 at multiplicities of infection of 100 and 20 plaque-forming units per cell, respectively. Infection with either virus prevented the aggregation of cells into smooth, spheroidal, spontaneously beating aggregates. Virus infection also caused a loosening of peripheral cells in aggregates formed from initially uninfected cells. Measurements were made of the rate of attachment of labeled single heart cells to a monolayer of like cells (homotypic), to HEP-2 cells (heterotypic), or to a plastic substrate (nonspecific adhesion). Infection caused a decline in homotypic adhesiveness to 20% of controls for HSV-1 and 10% of controls for HSV-2 and a decline in nonspecific adhesiveness to 75% of controls for both viruses, but no alteration in heterotypic attachment rates. These findings indicate that virus-induced cell-surface changes related to cell adhesion can be quantified by techniques measuring attachment rates. (45 refs)

**78-1652 Production of Plasminogen Activator by Cells Transformed by Herpesviruses.** (Eng) Howett, M. K. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033); High, C. S.; Rapp, F. *Cancer Res* 38(4): 1075-1078; 1978.

The production of plasminogen activator in a number of transformed cell lines was examined. Plasminogen activator was produced by hamster embryo fibroblasts transformed by herpes simplex virus (HSV) and cytomegalovirus, as determined by lysis of fibrin overlays in these cultures. Clonal variation was observed in the HSV-1- and HSV-2-



transformed lines. Normal hamster embryo fibroblasts and a hamster cell line transformed by PARA-7 (an adenovirus-simian virus 40 hybrid) did not lyse the fibrin. The human cell line TE-85 clone F-5, derived from a human osteogenic sarcoma, failed to produce plasminogen activator, but two separate clones of these cells that were morphologically transformed after exposure to UV-inactivated HSV-2 produced rapid lysis of the overlay. Experiments with normal dog serum depleted of plasminogen indicated the plasminogen dependence of the observed reaction. In another experiment, a fibrin overlay of lytically infected secondary rabbit kidney cells did not show induction of lysis during the time course of productive infection. It is suggested that plasminogen activator detection may serve as a convenient assay for transformation of normal cells by HSV. (18 refs)

**78-1653 Stimulation of Ornithine Decarboxylase (ODC) Activity by Human Cytomegalovirus (CMV) Infection (Meeting Abstract).** (Eng) Isom, H. C. (Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033). *Proc Am Assoc Cancer Res* 19: 24; 1978. (no refs)

**78-1654 Partial Characterization of the Proteins of Human Papilloma Viruses (HPV) 1-3.** (Eng) Pfister, H. (Zentrum für Hygiene, Institut für Virologie der Universität Freiburg, Hermann-Herder-Strasse 11, D-78 Freiburg, W. Germany); Gissmann, L.; zur Hausen, H. *Virology* 83(1): 131-137; 1977.

The protein compositions of full and empty particles of human papilloma viruses (HPV) 1, 2, and 3 (isolated from warts) were compared by sodium dodecyl sulfate-gel electrophoresis. The protein patterns revealed a considerable variation in the relative concentrations of three major virus proteins (VP2, 3, and 4) in preparations from individual warts. Cesium chloride equilibrium centrifugation showed that in some cases, heavy and light full particles prepared from the same wart showed a similar variability in the concentrations of VP2, 3, and 4. The different protein patterns probably result from the conversion of VP2 into VP3 and VP4. The molecular relationship of these three proteins was confirmed by BrCN cleavage, which led to the corresponding oligopeptides. Electron micrographs of the empty particles revealed that the only detectable protein components, VP3 and VP4, are present in typical capsomeres. The reason for the conversion of VP2 to VP4 is unknown. (13 refs)

**78-1655 Comparison of Epidermodysplasia Verruciformis (Lewandowsky-Lutz Disease) with Papovavirus Acanthomas by Light and Electron Microscopy.** (Ger) Kaufmann, J. (Dermatologische Universitätsklinik Zu-

rich, Gloriastrasse 31, CH-8091 Zurich, Switzerland); Me C.; Ott, F. *Arch Dermatol Res* 261(1): 39-54; 1978.

The cytological findings obtained for 300 common warts, condylomata acuminata and for primary eruptions of typical and seven questionable cases of epidermodysplasia verruciformis are presented. All specimens contained papovavirus particles. Four cytological patterns were distinguished among these growths: (1) intracytoplasmic intranuclear eosinophilic inclusion bodies, (2) condensation of the keratohyaline granules, (3) keratinocyte vacuolization as perinuclear halo and pyknosis, and (4) basophilic foamy giant keratinocytes. Patterns 1-3 were found in the common warts and condylomata acuminata, but pattern 4 was the characteristic feature in all cases of epidermodysplasia verruciformis. These findings and the literature data indicate that cytological pattern 4 is a specific to epidermodysplasia verruciformis. It is not certain whether the keratinocytes showing typical changes are always identical to virus-infected cells. The basophilic foamy giant keratinocytes can also occur in malignant epidermodysplasia verruciformis, in which they may participate in the dysplastic processes. (95 refs)

**78-1656 Microfluorometric Analysis of Complement and Indirect Immunofluorescence Tests for Human Papovavirus (JCV and BKV) T Antigen.** (Eng) Beth, E. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Cikes, M.; Giraldo, G. *J Cancer* 21(1): 1-5; 1978.

The indirect immunofluorescence (IIF) test was compared with the anticomplement immunofluorescence (ACIF) test using two hamster lines, HJC-15 and BK-L3, transformed by human papovaviruses JCV and BKV, respectively. Specific T-antigen staining was significantly stronger in the ACIF than in the IIF test. At antibody dilutions of 1:20 the former was 34 and 94 times more sensitive than the latter in the detection of JCV T and BKV T antigen. Sera from hamsters inoculated with serial transplantable HJC-15 and BK-L3 lines were tested for anti-T reactivity. In animals bearing stage two HJC-15 tumors, anti-T antibody activity could be detected only at late stages of tumor development. Anti-T reactivity with IIF titers  $\geq 1:80$  was obtained in 3 hamsters with tumors of up to three transplant generations. The percentage of animals with these titers declined during late passages. Only 22/70 animals with tumors of 4-12 transplant generations had high titers. Similar results were obtained in hamsters with BK-L3 tumors. A comparison between IIF and ACIF antisera titration methods revealed a one- to two-fold difference between the two methods. (refs.)

**78-1657 Stable Transformation of Mouse, Rabbit and Monkey Cells and Abortive Transformation of Human Cells.**



man Cells by BK Virus, a Human Papovavirus. (Eng) Tolani, M. (Inst. Microbiology and Virology, Univ. Bologna Via San Giacomo, 12, 40126 Bologna, Italy); Borgatti, Corallini, A.; Cassai, E.; Grossi, M. P.; Barbantidano, G.; Possati, L. *J Gen Virol* 38(2): 369-374; 1978.

Transformation experiments were performed on kidney, and liver cells of New Zealand white rabbits, kidney cells of Swiss or BALB/c mice, kidney cells of rhesus monkey and human embryonic fibroblasts, using BK virus (V). Transformation assays were performed at an input multiplicity of 10 fluorescent antibody focus-forming units per cell. Semipermissive mouse, rabbit, and monkey cells were stably transformed by the virus, and the specificity of transformation was demonstrated by the presence of BKV antigen in the nuclei of transformed cells and by virus release with Sendai virus-mediated fusion or transfection. Permissive human cells were only abortively transformed by BKV, since morphologically modified cells persisted in culture for a few passages and eventually died. Swiss strain mouse cells produced tumors when injected sc in newborn mice. Transformed BALB/c, rabbit, and monkey cells were nononcogenic. (19 refs)

78-1658 **Analysis of Human Tumors and Human Malignant Cell Lines for BK Virus-specific DNA Sequences.** (Eng) Wold, W. S. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, 3681 Park Ave., St. Louis, MO, 63104); Mackey, J. K.; Brackmann, K. H.; Takemori, N.; Green, M. *Proc Natl Acad Sci USA* 75(1): 454-458; 1978.

Extracts from 166 human tumors and 7 malignant cell lines were assayed for the DNA sequences of BK virus (BKV), a human papovirus, in molecular hybridization reactions with the BKV <sup>32</sup>P-DNA probes. The tumors included cancers of the digestive system (53), lung (45), prostate (5), bladder (25), kidney (25), brain (7), skin (3), melanomas (17), and lymphomas (17). Hybridization analysis of BKV-transformed hamster cell DNA indicated that the cells contained five to ten copies of 88% of the BKV genome per cell. All human cell lines, normal tissues, and tumors hybridized with BKV DNA. Apart from this homology, no BKV DNA sequences were detected in normal human tissues (kidney, spleen, lung, skin, ileum, rectum, and colon) or in any of the 166 tumors, which represented about 50% of all cancers in the US. Similarly, the BKV sequences were not detected in the malignant cell lines (melanomas, lung carcinomas, rhabdomyosarcoma, and glioblastomas). Although BKV infection is widespread, the virus apparently is not a major cause of cancer. (31 refs)

78-1659 **Virus Rescue from a T Antigen Negative Clone of BK Virus Transformed Hamster Cells (Meeting Abstract).** (Eng) Olive, M. (Dept. Radiology-Radiation

Therapy, Loyola Univ. Medical Center, Maywood, IL, 60153); Major, E. *Proc Am Assoc Cancer Res* 19: 131; 1978. (no refs)

78-1660 **Presence of a Transforming Agent in a Human Sarcoma Cell Line (HUS-2) (Meeting Abstract).** (Eng) Chapman, A. L. (Univ. Kansas Medical Center, Coll. Health Sciences and Hosp., Kansas City, KS, 66103); Morse, P. A. *Proc Am Assoc Cancer Res* 19: 125; 1978. (no refs)

78-1661 **Search for RNA Tumor Virus-related Nucleic Acids in Human Neoplastic Cells (Meeting Abstract).** (Eng) East, J. L. (Dept. Molecular Carcinogenesis and Virology, Univ. Texas System Cancer Center M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Knesek, J. E.; Seman, G.; Chan, J. C.; Dmochowski, L.; Bowen, J. M. *Proc Am Assoc Cancer Res* 19: 50; 1978. (no refs)

78-1662 **The Detection in Human Breast Carcinomas of an Antigen Immunologically Related to Glycoprotein (gp52) of the Mouse Mammary Tumor Virus (Meeting Abstract).** (Eng) Keydar, I. (Inst. Cancer Res., Columbia Univ., New York, NY, 10032); Mesa-Tejada, R.; Ohno, T.; Ramanarayanan, M.; Spiegelman, S. *Proc Am Assoc Cancer Res* 19: 64; 1978. (no refs)

78-1663 **An Increased Incidence of Lymphoma in Mice Inoculated with Human Breast Cancer Extracts.** (Eng) Basombrio, M. A. (Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Melo 3081-1425 Buenos Aires, Argentina); Mayer, A. M.; Rivell, C. *Arch Geschwulstforsch* 47(8): 679-684; 1977.

The presence of oncogenic viruses in fresh human mammary cancer specimens was investigated using a modified bioassay for mouse mammary tumor virus (MMTV). Specimens of human mammary cancer and normal or fibrocystic human mammary tissue were used. Each female (BALB x DBA/2)F<sub>1</sub> mouse received three injections of aqueous tissue extract, the first within 24 hr after birth, the other two within the first 2 mo of life in doses of 0.1, 0.15, and 1 ml, respectively, and the incidence of mammary tumors was recorded for 18 mo. The incidence of spontaneous mammary tumors in untreated test mice was very low (<1%) and was not increased by the injection of extracts from either human mammary cancer or normal or fibrocystic mammary tissues. However, the number of hyperplastic alveolar nodules (HAN) showed a statistically significant increase in the groups treated with either normal or neoplastic human breast tissues compared to un-



treated controls, but no difference was detected between the normal and the neoplastic extracts in this respect. The human mammary cancer extracts had a definite lymphomagenic effect: 39/173 mice that received these injections developed lymphomas compared to 9/147 animals that received normal human mammary gland extracts. The findings suggest that the lymphomagenic effect in the human extracts is that of an enhancer rather than that of an inducer and that it becomes significant when exerted on a preexisting background of spontaneous lymphomas, as found in (BALB/c x DBA/2)F<sub>1</sub> mice. (13 refs.)

- 78-1664 Association of C-Type Virus-Like Particles with Mitochondria (Meeting Abstract).** (Eng) Benjamin, I. (Pathology Dept., Medical Sch., St. Louis Univ., St. Louis, MO, 63104); Narconis, R.; Rana, M. W.; Thornton, H.; Pinkerton, H. *Fed Proc* 37(3): 334; 1978. (no refs)

- 78-1665 Fidelity Transcription of 5.5S RNA in a Human Cell-Free System Directed by Adenovirus DNA (Meeting Abstract).** (Eng) Wu, G. (Dept. Microbiology, Chemistry and Cancer Center, Emory Univ., Atlanta, GA, 30322). *Proc Am Assoc Cancer Res* 19: 228; 1978. (no refs)

- 78-1666 Adenovirus Deoxyribonucleic Acid Replication. Isolation of a Soluble Replication System and Analysis of the In Vitro DNA Product.** (Eng) Yamashita, T. (Inst. Molecular Virology, Saint Louis Univ. Sch. Medicine, St. Louis, MO 63110); Arens, M.; Green, M. *J Biol Chem* 252(22): 7940-7946; 1977.

A cell-free system for examining DNA replication was prepared from cultured KB cells late after infection with human adenovirus type 2 (Ad2), and the DNA product was characterized. The endogenous DNA polymerase activity in the culture was 10 to 34 times higher than the activity in uninfected cell cultures. DNA polymerase activity was enhanced by the addition of citrate, with max activity (sevenfold increase) occurring with 30 mM citrate. Sedimentation studies suggested that a complex sedimenting at 70S in 340 mM citrate is the soluble Ad2 DNA replication complex. Hybridization to Ad2 DNA revealed that the in vitro product is exclusively viral. The optimal pH for the enzyme ranged from 7.5 to 8.5; neither KCl nor ATP was required for activity. The optimal Mg<sup>2+</sup> concentration was 20 mM in the presence of 30 mM citrate, and all four deoxyribonucleoside triphosphates were required for max activity. DNase completely inhibited the reaction; actinomycin D and sodium pyrophosphate inhibited it 72% and 86%, respectively. The DNA products of the purified enzyme complex formed in a 1-min reaction cosedimented with viral 31S DNA; the remainder sedimented from

31S to 55S. After a 60-min chase with unlabeled deoxythymidine triphosphate, all the labeled product sedimented at 31S. CsCl density centrifugation revealed that the in vitro replication was semiconservative. (30 refs.)

- 78-1667 Initiation of Transcription in Nuclei Isolated from Adenovirus Infected Cells.** (Eng) Vennstrom, B. (Dept. Microbiology, Biomedical Center, Uppsala Univ., Uppsala, Sweden); Pettersson U.; Philipson, L. *Nucleic Acids Res* 5(1): 205-219; 1978.

The initiation of adenovirus-specific transcription was studied by introducing label in the 5' termini of the RNA from adenovirus 2-infected HeLa cell nuclei. B-<sup>32</sup>P guanosine triphosphate (GTP) and B-<sup>32</sup>P ATP were used. Specific terminal labeling occurred only with B-<sup>32</sup>P GTP. Nucleotide analysis of the RNA showed that the label is incorporated exclusively into pppGp and ppGp. The label from B-<sup>32</sup>P ATP was incorporated primarily into the 5' phosphate of the 5',3'-mononucleoside diphosphates (67%), with a preference for pAp. Some label was also detected in the 3'-nucleoside monophosphates (11%), pppAp (17%), and pppGp (5%). Analysis of the RNA synthesized in the presence of 1 or 10 µg/ml α-amanitin showed that only RNA polymerase II initiates virus-specific transcription in isolated nuclei. The virus-specific transcripts containing pppAp and pppGp in their 5' termini were identified as the 5.5S and 5.2S viral RNA species by hybridization and fingerprinting. (20 refs.)

- 78-1668 Adenovirus Deoxyribonucleic Acid Replication. Characterization of the Enzymatic Activities of a Soluble Replication System.** (Eng) Arens, M. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO 63110); Yamashita, T.; Panamanabhan, R.; Tsuruo, T.; Green, M. *J Biol Chem* 252(22): 7947-7954; 1977.

The enzyme activities of a 70S soluble viral DNA replication complex isolated from adenovirus 2 (Ad2)-infected KB cells were examined. Electrophoresis revealed at least 18 peaks in the crude complex compared to 6 major proteins in the purified complex. The major protein in the latter was a single stranded DNA-binding protein with a mol wt of 75,000. DNA polymerase activity was completely inhibited by 1 mM N-ethylmaleimide, thus excluding the possibility of the β form being present (the β form is not completely inactivated by purification). Studies of template-primer specificity and degree of inhibition by p-hydroxymercuribenzoate and a phasic double reciprocal plot for the determination of K<sub>m</sub> values of deoxythymidine triphosphate indicated that the polymerase activity was probably due to a 2:1 mixture of the α and γ forms. RNA polymerase activity consisted predominantly of polymerase II with significant levels of polymerase III. DNA ligase activity and low but significant RNase activity were also present. The solubilized preparation did not



tain significant amounts of DNA endonuclease of deoxyribonuclease. (38 refs.)

669 **Adenovirus Type 2 Late mRNA's: Structural Evidence for 3'-Coterminal Species.** (Eng) Ziff, Rockefeller Univ., New York, NY, 10021; Fraser, N. *J* 25(3): 897-906; 1978.

late messenger RNA (mRNA) products of adenovirus 2-infected HeLa cells were investigated using cells labeled with  $^{32}\text{P}$ O, 14-17 hr postinfection. The viral mRNA's isolated by chromatography and fingerprinted. Autoradiography of the mRNA products revealed three bands of approx mobilities of 26S, 21S, and 18S. These bands had two large characteristic T1 oligonucleotides in common as indicated by fingerprints of their 3'-terminal sequences. Mapping with restriction endonuclease indicated the 3' termini of these oligonucleotides were in the vicinity of coordinates 49-50.2 of the adenovirus type 2 DNA. It is concluded that the three mRNA's are coterminal in sequence at their 3' ends and that they overlap at internal positions. (40 refs)

670 **Induction of DNA Synthesis in Blocked ts Mutants of Hamster Cells by Adenovirus 2** (Meeting Abstract). (Eng) Rossini, M. (Temple Univ. Sch. Medicine, Philadelphia, PA, 19140); Weinmann, R.; Baserga, R. *Am Assoc Cancer Res* 19: 5; 1978. (no refs)

671 **Transformation with Specific Fragments of Adenovirus DNAs. I. Isolation of Specific Fragments with Transforming Activity of Adenovirus 2 and 5** (Eng) Van der Eb, A. J. (Univ. Leiden, Lab. Physiological Chemistry, Sylvius Labs., Wassenaarseweg 72, Leiden, Netherlands); Mulder, C.; Graham, F. L.; Houweling, A. *Gene* 2(3/4): 115-132; 1977.

DNA of human adenoviruses 2 and 5 (Ad2 and Ad5) was cleaved by the restriction endonucleases *HsuI*, *BamHI*, *EcoRI*, and *SmaI*, and the resulting fragments were separated by agarose gel electrophoresis. Fragments were tested for their ability to transform primary baby rat kidney (BRK) cells. Fragments with transforming activity were obtained with *R.EcoRI* (fragments A), *BamHI* (fragments B of Ad2 and A of Ad5 DNA), and *HsuI* (fragments C). These fragments represent the left terminal fragments of the respective restriction endonuclease cleavage products. The smallest fragment containing transforming activity was the *HsuI* G fragment (mol wt  $1.7 \times 10^6$  for both Ad2 and Ad5), which represented 7.3% of the viral genome. The transforming activity of Ad2 and Ad5 DNA's was abolished by digestion with *R.HpaI* and *SmaI* (which cleave at 4.3% and 1.3%, respectively), indicating that these enzymes cleave

into an area essential for transformation. All viral DNA fragment-transformed cell lines grew to only a very low level in 0.33% agarose medium (cloning efficiency < 1%), regardless of the size of the transforming fragment. All transformed cell lines reacted with antiserum against adenovirus subgroup-C-specific tumor (T) antigen, as detected by immunofluorescence. The T-antigen pattern in the *HsuI* G-transformed cells was atypical and differed from the usual pattern. Selection of *HsuI* G-transformed cells in 0.33% agarose medium resulted in cell populations containing the typical adenovirus T-antigen pattern, indicating that information for T antigen is present in *HsuI* G-transformed cells. (19 refs)

78-1672 **Characterization of Adenovirus-associated Virus-induced Polypeptides in KB Cells.** (Eng) Buller, R. M. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014); Rose, J. A. *J Virol* 25(1): 331-338; 1978.

Adenovirus-associated virus (AAV)-induced polypeptides were characterized in vivo, and a probable mechanism for their synthesis was determined. Polyacrylamide gel electrophoresis of KB cells coinfecting with AAV type 2, a defective parvovirus, and adenovirus type 5 as helper revealed the synthesis in vivo of five AAV-specific polypeptides. The three largest polypeptides, with a mol wt of 90,700, 71,600, and 60,000 daltons, respectively, comigrated in polyacrylamide gels with the three AAV structural polypeptides. The other two polypeptides had a mol wt of 24,900 and 15,800 daltons, respectively. The concentrations of the AAV-induced polypeptides relative to one another remained constant during the infectious cycle, and the structural polypeptides were present in the same proportions as those found in purified virions. Pulse-chase experiments using short pulses of radioactivity indicated that all polypeptides were generated at the level of protein synthesis and not by posttranslation proteolytic processing. Inhibitors of proteolytic enzymes did not influence the pattern of AAV-induced polypeptides, but L-canavanine, an amino acid analog, blocked the appearance of the major structural (60,000 daltons) and the larger nonstructural (24,900 daltons) polypeptides. These results suggest that AAV synthesizes its polypeptides by a proteolytic cleavage mechanism that operates at the level of nascent polypeptide synthesis. (25 refs.)

78-1673 **Transformation with Specific Fragments of Adenovirus DNAs. II. Analysis of the Viral DNA Sequences Present in Cells Transformed with 7% Fragment of Adenovirus 5 DNA.** (Eng) van der Eb, A. J. (Lab. Physiological Chemistry, Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands); Houweling, A. *Gene* 2(3/4): 133-146; 1977.

Five independently isolated clones of rat kidney cells trans-



formed by a small restriction endonuclease fragment of adenovirus 5 (Ad5) DNA (fragment *HsuI* G, which represents the left terminal 7% of the adenovirus genome) were analyzed with respect to the viral DNA sequences present in the cellular DNA's. The renaturation kinetics of <sup>32</sup>P-labeled specific fragments of Ad5 DNA was measured in the presence of a large amount of DNA extracted from transformed or untransformed cells. The fragments were produced by digestion of the <sup>32</sup>P-labeled Ad5 DNA with the endonuclease R *HsuI*, or by digestion of the <sup>32</sup>P-labeled fragment *HsuI* G of Ad5 DNA with R *HpaI*. All five transformed cell lines contained DNA sequences homologous to 75%-80% of *HsuI* fragment G only. Between 5 and 50 copies of fragment G were detected per diploid amount of cell DNA. The results indicate that a viral DNA segment as small as 5.5% of the Ad5 genome contains sufficient information for the maintenance of transformation. (11 refs)

**78-1674 Influence of Differential Hypothermia on Transplanted Hamster Tumor. II. Study of Adenovirus Type 12-induced T-Antigen by Immunofluorescence Technique.** (Jpn) Oohashi, T. (Dept. Neurosurgery, Okayama Univ. Medical Sch., Shikada-cho, Okayama 700, Japan). *Okayama Igakkai Zasshi* 89(7/8): 979-994; 1977.

The T antigens of transplanted hamster tumors induced by human adenovirus type 12 were studied by the fluorescent antibody technique within 24 hr of differential hypothermia (DH) treatment, in which one cheek pouch tumor was warmed at 37 C under generalized body hypothermia and the other was warmed at 20 C for 10 hr. A high proportion of the viable cells in the control tumors demonstrated three types of specific fluorescent staining. The most striking and consistent pattern was the presence of numerous fluorescent particles in the cytoplasm. The second type of fluorescence was fluorescent particles in the nucleus in addition to the cytoplasmic staining, and the third type was homogeneous staining of the nucleus. Immediately after DH, the tumor cells showed decreased fluorescent staining, especially that of the granular particles in the cytoplasm. Random flecklike and homogeneous nuclear staining was observed at 10 and 15 hr after DH treatment, when hematoxylin-eosin and nucleic acid staining revealed necrobiosis of the tumor cells. No fluorescence was observed 20 and 24 hr after DH. It is suggested that the cytoplasmic granular fluorescence diminished because DH affected the thermosensitivity of T antigen and/or inhibited T antigen production. The loss of flecklike and homogeneous nuclear fluorescence was due to DH-induced tumor cell necrosis. (81 refs)

**78-1675 The Transforming DNA Sequence Common to Highly Oncogenic Human Adenoviruses, Types 12, 18 and 31.** (Eng) Fujinaga, K. (Dept. Molecular Biology, Cancer Res. Inst, Sapporo Medical Coll., Sapporo 060, Japan); Ojima, S.; Yano, S.; Shinagawa, M. *Proc Jpn Acad* 53(4): 152-155; 1977.

An attempt was made to find a common transforming gene sequence among the highly oncogenic subgroup A human adenoviruses Ad12, Ad18, and Ad31. Ad7, from the weakly oncogenic subgroup B, and Ad2 and Ad5, from the transforming subgroup C, were included in the study for comparison. Ad12 DNA was cleaved by restriction endonuclease (Endo)-*HindIII* into 16 fragments, and fragment G was separated from the others by agarose gel electrophoresis and purified. The purified fragment, which had a mol wt of 1.6 x 10<sup>6</sup> daltons and was located at the left 7.2% of the viral genome, had the ability to transform a clonal rat embryo cell line, 3Y1. The resulting transformed cells, GY-1, which induced tumors in rats, synthesized tumor antigen and contained viral DNA sequences in their cell DNA, indicating that fragment G harbors the transforming gene(s) of Ad12. <sup>3</sup>H-labeled *doR-HindIII* fragments were hybridized with the DNA of Ad2, Ad5, Ad7, Ad12, Ad18, and Ad31 on a nitrocellulose membrane filter. Fragment G hybridized as efficiently with the DNA's of Ad18 and Ad31 as it did with Ad12 DNA. However, there was no significant hybridization with Ad5, or Ad7. The results strongly suggest that a unique transforming gene sequence(s) exists among all three subgroup A adenoviruses and that a very closely related or identical protein(s) is involved in the tumorigenesis by these adenoviruses. (10 refs)

*See also:*

- \*(Rev.): 78-1249, 78-1250, 78-1251, 78-1252, 78-1253, 78-1254, 78-1255, 78-1256, 78-1257, 78-1258, 78-1272.
- \*(Chem.): 78-1309, 78-1353, 78-1390, 78-1391, 78-1514.
- \*(Immun.): 78-1678, 78-1681, 78-1682, 78-1683, 78-1693.
- \*(Path.): 78-1713, 78-1720, 78-1731, 78-1732, 78-1742, 78-1744.
- \*(Epid.-Biom.): 78-1754, 78-1771.



1676 **Detection of Cytotoxic T-Lymphocytes in Tumour Bearing Animals: Procedures to Isolate Fully Active Populations.** (Eng) Vasudevan, D. M. (Dept. Chemistry, Medical Coll., Kozhikode-673 008, India); Jayakumar, T. *Indian J Cancer* 14(4): 354-360; 1977.

Spleen cells from lymphoma-bearing DBA mice were selected for their cytotoxic activity against labeled target cells. A three-step procedure of preincubation for 24 hr at 37.5 C, bovine serum albumin (BSA)-gradient centrifugation and selection of low-density lymphocytes (density  $< 1.08 \text{ g/cm}^3$ ), velocity sedimentation to select the larger sized lymphocytes (cell diameter  $10\mu$ ) resulted in a 1,000-fold enrichment in cytotoxic activity, even though the final cell population consisted of only 0.25% of the original spleen cells. The selected cells are predominantly T cells, as indicated by the  $^{51}\text{Cr}$ -release assay. The supernatant fluid from the preincubation mixture abrogated the cytotoxicity of the fully active lymphocytes, indicating that the preincubation procedure removes blocking factors (antigen, antibody, or immune complexes) from the surface of the lymphocytes. (12 refs)

1677 **Immunological Changes of the Lymphocyte Population with Advancing Age.** (Ger) Heilmann, E. (Medizinische Universitätsklinik, Westring 3, 4800 Munster/Westfalen, W. Germany); Rex, B. *Schweizer Wochenschr* 107(48): 1776-1778; 1977.

Lymphocyte populations of 90 clinically healthy subjects (men, 47 women) aged 9 mo to 90 yr were investigated. There were 10 persons in each 10-yr age bracket. The total lymphocyte count decreased with age, being highest in children (52%) and lowest in adults aged 81-90 yr (34.4%). The proportion of T lymphocytes dropped from 71% in children to 18% in adults aged 81-90 yr, but the proportion of B lymphocytes increased from 7% to 23%; the absolute B-cell count remained practically unchanged. In children, the number of rosette-forming T lymphocytes was nearly the same with and without the addition of neuraminidase. Reduction of the T-cell count in senescence is attributed to involution of the thymus; this reduction probably causes the decreased cellular immunity that occurs in old age. T cells are able to transform into killer cells to eliminate tumor cells. The findings support the immune surveillance theory of tumor pathogenesis and explain the increased cancer incidence in old age. (10 refs.)

78-1678 **Blastogenic Response of Purified Human T-Lymphocyte Populations to Epstein-Barr Virus (EBV).** (Eng) Gergely, P. (II Dept. Medicine, Semmelweis Univ., Budapest, Hungary); Ernberg, I.; Klein, G.; Steinitz, M. *Clin Exp Immunol* 30(3): 347-353; 1977.

The effect of Epstein-Barr virus (EBV: strain B95-8) on the blastogenesis of purified T cells was studied following different forms of antigen presentation. T cells were obtained from the cord blood or from the peripheral blood of EBV-seropositive and -seronegative adults or from patients with acute infectious mononucleosis (IM). The addition of virus increased the labeled thymidine uptake of unfractionated lymphocytes from seropositive and seronegative subjects and from cord blood, but not from patients with IM. The virus also evoked a slight response in purified T cells from seropositive donors, but not in T cells from the other sources. The addition of autologous B cells with EBV adsorbed on their surfaces caused a more significant blastogenic response. This response was even more pronounced in the presence of  $5 \times 10^{-5}$  mole/ml mercaptoethanol. Addition of  $1 \mu\text{g/ml}$  phytohemagglutinin caused a significant increase in DNA synthesis in both the unfractionated and pure T-cell populations. It is suggested that in vivo-primed T cells respond in vitro with increased blastogenesis, although the antigens responsible for the stimulation need further study. (31 refs)

78-1679 **T- and B-Lymphocyte Subpopulations in Preinvasive and Invasive Carcinoma of the Cervix.** (Eng) Rand, R. J. (Leeds LS2 9NG, England); Jenkins, D. M.; Bulmer, R. *Clin Exp Immunol* 30(3): 421-428; 1977.

Changes in T- and B-lymphocyte subpopulations were studied in 28 women with invasive squamous cervical carcinoma, 21 women with cervical carcinoma in situ, 12 women with cervical dysplasia, 20 patients with other gynecologic disorders, and 51 controls to determine if changes in immune status are related to the progression of cervical carcinoma. There was a significant depression in T cells in association with invasive but not preinvasive cervical carcinoma. B cells detected by erythrocyte-antibody-complement rosette formation were significantly raised in patients with invasive cancer but not in patients with preinvasive cancer. Surface membrane immunoglobulin (SMIg)-bearing B cells were not significantly altered by the malignant disease. The T- and B-lymphocyte changes were more marked in patients with extensive cancers. It is suggested that a subpopulation of masked T cells escaped detection as rosette-forming cells and



was included in the SMIg-bearing B cells. Furthermore, since the patients were not matched for age, age-related T- and B-cell changes may account for the findings in the relatively aged (mean 50 yr) patients with invasive cancer. (47 refs)

- 78-1680 Proliferative Responsiveness of Two Distinct Human T-Cell Subpopulations to Con A, PHA and Alloantigens.** (Eng) Webb, S. R. (Dept. Pediatrics, Univ. Alabama in Birmingham, Birmingham, AL 35294); Lydyard, P. M.; Moretta, L.; Ferrarini, M.; Mingari, M. C.; Moretta, A.; Cooper, M. D. In: *Regulation Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York): Academic Press, Inc.: 825 pp.; 512-514; 1977.

Two human T-cell subpopulations, T<sub>γ</sub>, which bears receptors for the Fc portion of IgG, and T<sub>μ</sub>, with receptors for IgM, were cultured with various concentrations of the T-cell mitogens concanavalin A (Con A) and phytohemagglutinin (PHA). Measurements of <sup>3</sup>H-thymidine uptake indicated that both fractions responded similarly to Con A, but not to PHA. T<sub>γ</sub> responded poorly to all PHA concentrations, with a peak response occurring at low concentrations; T<sub>μ</sub> responded well, but only to high PHA concentrations (10-20 times that required for T<sub>γ</sub>). Experimental results also suggest a synergistic interaction of T-cell subsets when the T-cell populations are responding together to PHA. In the presence of alloantigens, both populations were also capable of proliferating in a oneway mixed lymphocyte culture. (8 refs.)

- 78-1681 Level of Humoral Immune Response Capability vs the Sensitivity of Target Cell Populations in the Determination of Resistance to Murine Viral Leukemogenesis (Meeting Abstract).** (Eng) Meredith, R. F. (Allegheny General Hosp., Pittsburgh, PA, 15212). *Proc Am Assoc Cancer Res* 19: 49; 1978. (no refs)

- 78-1682 Decreased T Cell Levels in Patients with Warts.** (Eng) Chretien, J. H. (Student Health Service, Georgetown Univ., Washington, DC, 20057); Esswein, J. G.; Garagusi, V. F. *Arch Dermatol* 114(2): 213-215; 1978.

T-cell levels were determined in 72 healthy patients with viral warts, 21 patients who had been cured of warts 1-15 yr previously, and 35 age-matched controls with no history of warts to compare the immune status of the groups and changes that might occur with treatment of the warts. The mean percentage of lymphocytes that formed rosettes with sheep RBC was less in patients with warts and patients previously cured of warts than in normal controls. The number of T cells per

cubic millimeter was decreased in untreated patients with warts but was normal in patients cured of warts for > 1 yr. Furthermore, the morphology of the rosettes in the two patient groups differed from the controls: 32% had small numbers of sheep RBC bound loosely to T cells, compared with 91% in the controls. These T-cell abnormalities in patients with warts suggest a need for evaluating T-cell function in patients who are especially resistant to the usual therapy and a need for determining if these patients can be treated with immune-stimulating drugs. (16 refs)

- 78-1683 Role of T and B Lymphocytes in Tumor Growth.** (Rus) Petrov, R. V. (No affiliation given); Kiselev, R. M. *Vestn Akad Med Nauk SSSR* (10): 64-69; 1978.

The role of immune surveillance in tumor growth was evaluated. The immune response was studied in C57BL/6 (CBA x C57BL)F<sub>1</sub> mice with transplanted methylcholanthrene-induced carcinoma Ca-755, CBA mice inoculated with a syngeneic carcinoma of the uterine cervix, and C3H/He mice with spontaneous mammary gland tumors. Characteristic features of immunogenesis in tumor-bearing mice were a decreased number of stem cells in the bone marrow, an increased number of stem cells in the spleen, enhanced migration of stem cells from the bone marrow, a decreased number of B-cell precursors, inhibition of T- and B-lymphocyte cooperation, elevation of the suppressive effect of spleen cells, and unaltered killer effect of the T cells from lymph nodes. (18 refs.)

- 78-1684 Report of T and B Lymphocyte Inhibition of Macrophage Migration in Mice with Methylcholanthrene-induced Sarcomas.** (Spa) Galussio, J. (Laboratorio de Immunologia, Policlínico Santojuan, Buenos Aires, Argentina); Fridman, J. L.; Tessler, J. *Medicina (B Aires)* 37(3): 264-270; 1977.

The role of T and B cells in macrophage migration inhibition (MMI) was studied in BALB/c mice bearing sc sarcomas induced by 20-methylcholanthrene. Peritoneal exudate cells from these animals demonstrated MMI in the presence of tumor-specific antigens. The migration indices reached maximum values 9 days after grafting of the tumor, later declining to initial values on day 30. Spleen cells from normal mice immunized by resection of the tumor, and mice bearing 30-day sarcomas were then added to the peritoneal exudate cultures to determine which cells were responsible for abrogation of MMI. The immune spleen cells promoted migration inhibition when added to peritoneal cells from normal and tumor-bearing mice. However, spleen cells from the latter group abrogated the migration inhibition of immune peritoneal cells. The incubation of immune spleen cells with anti-theta serum inhibited these properties. Spleen



mice with 30-day tumors, incubated with anti-gamma in serum, lost their capacity to abolish MMI when ad- immune peritoneal exudate cells. (26 refs)

- 85 **The Importance of the Ratio Between Effector and Target Cells for Detection of Serum Block-Tumor Lymphocytolysis.** (Eng) Miller, F. R. (Dept. Microbiology, Univ. Wisconsin, Madison, WI); Blazkovec, A. A. *Immunol Commun* 7(1): 81-89;

significance of the effector to target cell ratio (E:T) in nship to the blocking capacity of tumor-bearer sera udied in vitro in Sewall Wright strain 2 guinea pigs with iethylnitrosamine-induced tumor. Thirty-three sera ested in 124 experiments in which the E:T ratio was Significant blocking of cell-mediated lysis occurred in f the experiments, but significant potentiation occurred y 7%. Six sera were found that showed significant ng in some experiments and significant potentiation in experiments. One of these sera was further evaluated ying the E:T, using lymphocytes from three immune s. For each of the three populations of immune lym- tes, significant blocking was demonstrable only at one e E:T tested. Blocking was observed only with an E:T 1 in two cases; in the third case, blocking was observed but potentiation was observed at 200:1. The effect of sera on lymphocytolysis in vitro is clearly dependent E:T ratio. (11 refs)

- 86 **Alterations in the Mitogen Responsiveness of Lymphocytes from Mice Bearing Moloney Sar-Virus Induced Tumors.** (Eng) Marshall, G. D. (Div. Chemistry, Dept. Human Biological Chemistry and Gen- Univ. Texas Medical Branch, Galveston, TX, 77550); an, G. B.; Foster, B. G.; Goldstein, A. L. *Immunol un* 6(6): 603-615; 1977.

astogenic responsiveness of lymphocytes from BALB/ was investigated during various phases of Moloney a virus-induced tumor growth. Lymphocytes from thymus, and lymph nodes were tested for responsive- phytohemagglutinin (PHA) and concanavalin A (Con ere was a significant decrease in PHA-induced blasto- of all lymphocytes tested at the time of max tumor e, with a return to normal responsiveness as the tumor ed. A differential dose-dependent Con A response oc- in spleen and thymus lymphocytes. A decreased <sup>3</sup>H- line uptake occurred at an optimal Con A dose, cor- g with the PHA decrease. However, at a lower Con , an increased response was observed, beginning short- re the PHA depression and continuing until regression tumor began. This effect was not seen in lymph node

lymphocytes. These events may be due to a population of Con A-responsive cells (probably lymphocytes) that migrate to and/or mature in the spleens of tumor-bearing animals prior to tumor regression. (17 refs)

- 78-1687 **Development and Persistence of Cytolytic T Lymphocytes in Regressing or Progressing Mo- loney Sarcomas.** (Eng) Gillespie, G. Y. (Dept. Pathology, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC 27514); Russell, S. W. *Int J Cancer* 21(1): 94-99; 1978.

The development and persistence of cytolytic T cells in re- gressing or progressing Moloney sarcomas in male BALB/c AnCr mice were examined. The regressing and progressing sarcomas were induced by im inoculation of  $5 \times 10^3$  and  $10^6$  MSC cells, respectively. The percentage of T cells recovered from regressing sarcomas were about twice that obtained from progressing sarcomas. Bi- phasic kinetic profiles of cytotoxic activity were almost identical for regressing and progressing tumors, but the cytotoxic activity developed at different times. In progressing tumors, activity was max between days 7 and 9 and was undetectable by day 13. In regress- ing tumors, max activity was not reached until day 13, and the tumors regressed by day 15. The cytotoxicity of T cells from draining lymph nodes was then studied. The num- ber of T cells in the draining nodes was increased four- to fivefold. Biphasic peaks of activity were observed for these T cells, but the cytotoxicity reached a max 1-2 days earlier and persisted 1-2 days longer than in the tumors themselves; these findings held for both tumor types. The lytic activity of these cells was lower than that of intratumoral T cells. Further studies indicated that the reduction in T-cell activity with sarcoma progression was due to an alteration in func- tional activity and not to interference in effector-target cell interaction. A 4-day culture of noncytotoxic T cells from re- gional nodes of progressive tumors increased their cytolytic activity to peak levels. The increase was diminished if MSC cell lysates, macrophages, or macrophages fed the lysates were present during culture. (16 refs.)

- 78-1688 **The Specificity of Spontaneous Cytotoxicity of Human Lymphocytes Before and After Culture (Meeting Abstract).** (Eng) Ortaldo, J. R. (NIH, Bethesda, MD, 20014); Bonnard, G. D.; Kind, P. H.; Herberman, R. B. *Proc Am Assoc Cancer Res* 19: 106; 1978. (no refs)

- 78-1689 **Suppression of Lymphocytic Anti-Tumor Cyto- toxicity by a T-Dependent Serum Factor (Meet- ing Abstract).** (Eng) Rao, P. E. (Cornell Univ. Medical Coll.



and Graduate Sch. Medical Sciences, New York, NY, 10021). *Proc Am Assoc Cancer Res* 19: 23; 1978. (no refs)

**78-1690 A Proposed Mechanism for Tumor Cell Lysis by Cytotoxic Lymphocytes (Meeting Abstract).** (Eng) Grimm, E. (Dept. Microbiology and Immunology, Univ. California Los Angeles, Los Angeles, CA, 90024); Price, Z.; Bonavida, B. *Proc Am Assoc Cancer Res* 19: 109; 1978. (no refs)

**78-1691 Polymorphonuclear Leukocyte Granule Mediated Cytotoxicity (Meeting Abstract).** (Eng) Pardridge, D. H. (Div. Oncology, Dept. Surgery, Sepulveda Veterans Hosp., Sepulveda, CA, 91343). *Proc Am Assoc Cancer Res* 19: 133; 1978. (no refs)

**78-1692 Inhibition by Normal Thymocytes of Antibody-dependent Cell-mediated Cytotoxicity Against Tumor Cells (Meeting Abstract).** (Eng) Lauer, S. (Midwest Children's Cancer Center, Milwaukee, WI, 53233); Casper, J. T.; Borella, L. *Proc Am Assoc Cancer Res* 19: 130; 1978. (1 ref)

**78-1693 T Cell Interactions for Maximal In Vitro Cytotoxicity of Syngeneic Mouse Mammary Tumors: Evidence for a Helper Defect in Mammary Tumor Virus (MTV) Infected Mice (Meeting Abstract).** (Eng) Stutman, O. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Shen, F. W. *Proc Am Assoc Cancer Res* 19: 59; 1978. (no refs)

**78-1694 Human Leukemia Cell Lines: Evidence for Differentiation Toward T- and B-Cell Axis Within a Leukemia Clone (Meeting Abstract).** (Eng) Minowada, J. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Oshimura, M.; Abe, S.; Greaves, M. F.; Janossy, G.; Sandberg, A. A. *Proc Am Assoc Cancer Res* 19: 109; 1978. (no refs)

**78-1695 Distribution and Immunochemical Properties of a Unique B-Cell Differentiation Antigen on Human Leukemic Lymphocytes (Meeting Abstract).** (Eng) Balch, C. M. (Univ. Alabama Medical Center, Birmingham, AL, 35294); Vogler, L. B.; Dougherty, P. A. *Proc Am Assoc Cancer Res* 19: 119; 1978. (1 ref)

**78-1696 Genetically Restricted Thymus-Derived Suppressor Lymphocyte Activity in the Bladder of a Bladder Cancer (Ca) Patient (Meeting Abstract).** (Eng) Bean, M. A. (Virginia Mason Res. Center, Seattle, WA, 98101); Kodera, Y.; Cummings, K. B. *Proc Am Assoc Cancer Res* 19: 136; 1978. (no refs)

**78-1697 The Immunocompetence of Tumor T Cells and Their Role in Generalized Immunosuppression and Immunostimulation Following Inoculation of Dimethylbenzanthracene-Induced Leukemia Virus in Mice.** (Eng) Roder, J. C. (Dept. Tumor Biology, Karolinska Inst., 104 Stockholm 60, Sweden); Tyler, L.; Ball, J. K.; Singhal, S. *Cell Immunol* 36(1): 128-142; 1978.

The mechanism of immunosuppression was studied in CF-1 D mice inoculated with a 7,12-dimethylbenz(a)anthracene-induced leukemia virus. The spleen cells from these mice exhibited a progressive decline in the in vitro response to heterologous RBC antigens in parallel with tumor growth. Since nonresponsiveness could be transferred to irradiated non-tumor-bearing mice with spleen cells and since T cells from tumor-bearing mice cooperated with normal bone marrow cells, but bone marrow from tumor-bearing mice did not cooperate with normal T cells, this immunodepression may involve a B-cell defect rather than extrinsic factors in the cellular environment. Furthermore, T cells from thymic tumor could cooperate with normal bone marrow cells upon transfer to irradiated recipients. TL 485-2 cells derived from this tumor could be specifically activated by sheep RBC, indicating that the virus-transformed T cells were immunocompetent. Suppressor cells, which appeared in the spleen concomitant with immunodepression and tumor development, may directly raise B-cell thresholds for dependent triggering signals, since the antibody response of spleen cells from tumor-bearing mice could be restored by *Escherichia coli* lipopolysaccharide, 2-mercaptoethanol, or cells exogenously preactivated in normal animals. The suppressor cell could be enriched by adherence to plastic, and it was removed by treatment with carbonyl iron. Transformed, virus-infected cells were not suppressive when added to spleen cells in vitro, but rather resulted in a marked, polyclonal enhancement of the plaque-forming cell (PFC) response. The interaction of TL 485-2 and normal spleen cells resulted in the release of a stimulatory factor that increased DNA synthesis in resting cells and increased PFC. (47)

**78-1698 T-Lymphocyte Variant of Hairy-Cell Leukemia.** (Eng) Saxon, A. (Dept. Medicine, Univ. of California, Sch. Medicine, Los Angeles, CA, 90024); Stevens, R. L.; Golde, D. W. *Ann Intern Med* 88(3): 323-326; 1978.

Hairy-cell leukemia cells from a 33-yr-old man was subjected to immunohematologic studies, and the results indicated



These cells had receptors for sheep RBC and, therefore, human T-cells characteristics. The cells did not have membrane receptors or immunoglobulin markers of B lymphocytes or monocytes, nor did they synthesize immunoglobulin. A lymphoid cell line established in vitro from these cells had the same T cell characteristics. The line was positive for tartrate-resistant acid phosphatase, formed rosettes with untreated sheep RBC, and reacted with an anti-T-cell antiserum. These findings indicate that hairy-cell leukemia may result from the clonal proliferation of T cells as well as the usual B cell clone. (24 refs)

**78-1699 Use of Stimulating Capacity of Mixed Lymphocyte Reaction (MLR-S) as a Possible Marker for the Cell-Origin of Null-Cell Acute Lymphoblastic Leukemia (Meeting Abstract).** (Eng) Han, T. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Minowada, J. *Proc Am Assoc Cancer Res* 19: 374; 1978. (no refs)

**78-1700 Studies on Heterotransplantation and Cloning of Two Human Leukemia Cell Lines Representing Myeloblasts in Chronic Myelocytic Leukemia and B-Cell Acute Lymphoblastic Leukemia (Meeting Abstract).** (Eng) Honjo, I. (Roswell Park Memorial Inst., Buffalo, NY, 14263). *Proc Am Assoc Cancer Res* 19: 109; 1978. (no refs)

**78-1701 Autologous Leukemia-specific T-Cell-mediated Lymphocytotoxicity in Patients with Acute Myelogenous Leukemia.** (Eng) Lee, S. K. (Dept. Immunology, Natl. Inst. Medical Res., London N7, England); Oliver, T. *J Exp Med* 147(3): 912-922; 1978.

Autologous leukemia-specific T-cell-mediated lymphocytotoxicity was studied in 14 patients with acute myelogenous leukemia, and the nature of the effector cell, the target antigen on the third-party cell, and the target antigen on the leukemia blast were investigated. Short-term culture of autologous lymphocytes from acute myelogenous leukemia patients with inactivated autologous leukemic blast cells plus allogeneic lymphocytes generated effector T lymphocytes which were cytotoxic for the specific autologous blast cell in 14 patients. Experiments using Daudi and Molt 4 lymphoblastoid cell lines as a third-party helper cell suggest that the H-2Dd compatibility antigen D locus incompatibility is necessary to provide effective help in this system. Cold target inhibition experiments, crossover studies between pairs of patients, and experiments with allogeneic leukemic blast cells priming stimulus suggest that the target antigen is only present on the specific autologous blast cell. Most animal models with a viral etiology have common tumor-specific antigens, whereas unique determinants have usually been found in virally induced tumors. The findings of this study plus

the failure of other investigators to isolate infectious viruses from human leukemias using techniques that easily detect viruses in animal tumors raise doubts about the role of viruses in the pathogenesis of human leukemia. (31 refs)

**78-1702 Lymphoma-cytotoxic Natural Killer Cells in Hamsters (Meeting Abstract).** (Eng) Datta, S. K. (Baylor Coll. Medicine, Houston, TX, 77030); Trentin, J. J.; Sinkovics, J. G. *Proc Am Assoc Cancer Res* 19: 193; 1978. (no refs)

**78-1703 Heterogeneity of Natural Killer (NK) Cells in Mice (Meeting Abstract).** (Eng) Bennett, M. (Dept. Pathology, Boston Univ. Sch. Medicine, Boston, MA, 02118); Luevano, E.; Kumar, V. *Fed Proc* 37(3): 363; 1978. (no refs)

**78-1704 Effect of Immunosuppressive Agents on Mouse Natural Killer Cells (Meeting Abstract).** (Eng) Djeu, J. Y. (Litton Bionetics, Inc., Kensington, MD, 20014); Heinbaugh, J. A.; Holden, H. T.; Herberman, R. B. *Proc Am Assoc Cancer Res* 19: 237; 1978. (no refs)

**78-1705 Detergent Solubilization of B-Lymphocyte Immunoglobulin.** (Eng) Lifter, J. (Memorial Sloan-Kettering Cancer Center, Walker Lab., Rye, NY 10580); Choi, Y. S. *Adv Exp Med Biol* 88: 99-107; 1977.

Cells isolated from the bursae of 5-day-old SC chicks and grown in <sup>3</sup>H-leucine were used to investigate whether or not detergent solubilization of membrane proteins affects experimental results by not disrupting some protein-protein interactions, thereby leading to contamination. Material isolated by serologic precipitation was studied further by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Cells were lysed by the detergent NP-40 and either (1) further solubilized by adding 20% deoxycholate (DOC) to a final concentration of 2%, maintained at 0 C for 30 min, and centrifuged for 60 min at 4 C to sediment ribosomes or (2) not treated with DOC. SDS-PAGE showed that a significant percentage of the radioactivity was associated with a protein(s) (approx mol wt 50,000 daltons) in the aliquot treated with NP-40 only. This protein migrated between the heavy and light chains and was virtually eliminated by DOC treatment. Because this coprecipitating protein was not found in an antiimmunoglobulin (anti-Ig) serologic precipitate of the DOC aliquot, it probably does not share the Ig class or subgroup antigenic determinants with the heavy and light chains



and it is not likely to be covalently linked to B-cell Ig. It is suggested that this protein is a 'proreceptor'. (18 refs.)

- 78-1706 Frequency of Lymphocytes Bearing Fc Receptors and Surface Membrane Immunoglobulins in Normal, Persistent Lymphocytotic and Leukemic Cows.** (Eng) Kumar, S. P. (Dept. Large Animal Clinical Sciences, Coll. Veterinary Medicine, Univ. Minnesota, St Paul, MN, 55108); Paul, P. S.; Pomeroy, K. A.; Johnson, D. W.; Muscoplat, C. C.; Van Der Maaten, M. J.; Miller, J. M.; Sorensen, D. K. *Am J Vet Res* 39(1): 45-49; 1978.

The frequency of lymphocytes bearing Fc receptors and surface membrane immunoglobulins (SIg) was assayed in the peripheral blood of 12 normal cows, 5 cows with persistent lymphocytosis (PL), 3 cows with adult lymphosarcoma, 1 heifer with thymic lymphosarcoma, and 1 steer with the skin form of leukemia. These diseases are thought to be caused by a C-type virus designated bovine leukemia virus (BLV). Fluoresceinated, heat-aggregated bovine immunoglobulins (B-IgG) and human immunoglobulins (H-IgG) bound to bovine peripheral blood lymphocytes, but H-IgG was more sensitive for the detection of Fc receptors. It is suggested that the B-IgG used in this study is lacking the IgG subclass that avidly binds to Fc receptors. Double-labeling experiments suggested that all Fc+ cells have SIg, a marker for B lymphocytes. The percentage of Fc+ and SIg+ lymphocytes in normal cows was 9.5% and 16.2%, respectively. PL cows had 2.71 times more Fc+ and 3.85 times more SIg+ lymphocytes than did normal cows. Animals with lymphosarcoma had a lower percentage of Fc+ and SIg+ cells than did cows with PL. Cows with thymic lymphosarcoma and those with the skin form of leukemia had normal percentages of Fc+ and SIg+ cells. These findings substantiate the presence of a B-cell abnormality in BLV infection. (36 refs)

- 78-1707 Antibody-Dependent Lymphocytotoxicity Induced by Immunoglobulin G from Hodgkin's Disease Splenic Lymphocytes.** (Eng) Longmire, R. L. (Dept. Hematology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037); Ryan, S.; McMillan, R.; Lightsey, A.; Heath, V. *Science* 199(4324): 71-72; 1978.

The IgG produced in cultures of splenic lymphocytes from patients with Hodgkin's disease bound to a population of homologous peripheral blood lymphocytes and initiated antibody-dependent cell cytotoxicity (ADCC) in cultures from 5/8 patients. The IgG produced by splenic lymphocytes from normal subjects and patients with non-Hodgkin's lymphomas failed to show this reaction. Two of the Hodgkin's disease patients whose cultures produced negative results in the ADCC test were in Stage IA, and there was involvement of

a single cervical focus. The third patient was in remission. The target cells appear to be T lymphocytes, and the effector cells bear Fc receptors that are inhibited by antigen-antibody complexes. The findings suggest that the circulating lymphopenia and deficient cell-mediated immune responses often seen in Hodgkin's disease may be due to the production of autoantibodies directed against T lymphocytes. Two factors may contribute to the systemic compromise of T-lymphocyte immunocompetence: (1) the amount of reactive IgG needed to produce ADCC is minimal compared to that required to bring about complement-dependent cytotoxicity; and (2) autoantibody is produced in some apparently uninvolved tissues (spleen) as well as in tissues with histologically recognizable Hodgkin's lesions. (17 refs)

- 78-1708 In Vivo and In Vitro Studies of a TNP-binding IgA Lymphoma Isolated from MOPC-315, TNP-binding IgA Plasmacytoma of BALB/c Mice (Meeting Abstract).** (Eng) Autry, J. R. (Washington Univ., St. Louis, MO, 63110); Gebel, H. M.; Dibner, J.; Lynch, R. G. *Fed Proc* 37(3): 486; 1978. (no refs)

- 78-1709 Mediation of Cytotoxic Functions by Classes and Subclasses of Sheep Antibody Reactive with Cell Surface Immunoglobulin Idiotype and Constant Region Determinants.** (Eng) Stevenson, F. K. (Tenovus Res. Lab. General Hosp., Tremona Road, Southampton SO9 4XY, England); Elliott, E. V. *Immunology* 34(2): 353-358; 1978.

Two sheep (Clun crossbreeds) were immunized with the light chain from guinea pigs in the terminal phase of L<sub>2</sub> leukemia and, following a booster injection 5 wk later, the animals were bled and the sera analyzed. Sheep antibodies reactive with either the idiotype or constant region antigen determinants of the immunoglobulin light chain on L<sub>2</sub> leukemia cells, were separated into IgM, IgG<sub>1</sub>, and IgG<sub>2</sub>. Antibody to both IgG subclasses inhibited the migration of L<sub>2</sub> cells along plastic surfaces; IgM was only weakly inhibitor. Antibody of class IgM and of subclass IgG<sub>1</sub> mediated complement cytotoxicity against L<sub>2</sub>C cells, but only that of subclass IgG<sub>2</sub> mediated K-cell cytotoxicity. The effector arms were rabbit complement and sheep peripheral WBC, respectively. (11 refs)

- 78-1710 Serum IgA and Emotional Expression in Breast Cancer Patients.** (Eng) Pettingale, K. W. (Fairbairn Court Unit, King's Coll. Hosp. Medical Sch., Denmark Hill, London S.E.5., England); Greer, S.; Tee, D. E. *J Pathol* 21(5): 395-399; 1977.



m immunoglobulins and expression of anger were mea-  
 d preoperatively in 160 women admitted consecutively  
 breast tumor biopsy between 1971 and 1973. All women  
 < 70 yr of age and had masses < 5 cm in diameter.  
 m IgA was significantly higher ( $p < 0.001$ ) in patients  
 extreme suppression of anger. Other serum immuno-  
 ulin levels did not differ significantly, and they were not  
 ed to any expression of emotion other than anger. Post-  
 atively, the 69 women with breast cancer and 91 women  
 benign disease were separated into diagnostic groups,  
 serum IgA was measured at 3 mo, 1 yr, and 2 yr. At each  
 w-up in both groups of patients, serum IgA levels were  
 er in patients with extreme suppression of anger.  
 he benign breast disease patients, these levels were  
 significantly higher preoperatively. In the breast  
 er patients, significant differences were noted

preoperatively and at 3 mo and 2 yr postoperatively.  
 There may be a psychobiological link in the patho-  
 genesis of breast cancer. (20 refs.)

*See also:*

\*(Rev.): 78-1257, 78-1258, 78-1259, 78-1260, 78-1261,  
 78-1273.

\*(Chem.): 78-1275, 78-1318, 78-1406, 78-1420,  
 78-1463.

\*(Phys.): 78-1524, 78-1539, 78-1544, 78-1547.

\*(Viral): 78-1555, 78-1559, 78-1568, 78-1569, 78-1574,  
 78-1576, 78-1578, 78-1581, 78-1587, 78-1594,  
 78-1599, 78-1615, 78-1623, 78-1636, 78-1637,  
 78-1641, 78-1643, 78-1644, 78-1648, 78-1656.

\*(Path.): 78-1740, 78-1745, 78-1751.



## PATHOGENESIS

- 78-1711 **Chronic Inflammation and the Basic Regulatory System.** (Ger) Perger, F. (Kaiser-Franz-Ring 8, A-2500 Baden, Austria). *Wien Med Wochenschr* 128(2): 31-37; 1978.

Similarities and relationships between malignant tumors and chronic inflammation are described in relation to Pischinger's basic regulatory system, which consists of reticulocytes, fibroblasts, capillary system, terminal nerve plexes, and extracellular tissue fluid, and the specific immune system. A considerable reduction or absence of reactivity is a common feature of both tumors and chronic inflammation: a congruent inhibition of the basal regulatory system was observed in both diseases. The similarities between chronic inflammation and malignant tumors also include irreversible loss of reactivity of the regulatory system, reduced oxyhemoglobin level in the venous blood, inhibition of cellular immunity, absence of the Freund-Kaminer reaction, and excessive lowering of the reactivity threshold. Inhibition of the basal regulatory system by chronic inflammation and other factors (clinically silent bacterial infection, disturbed wound healing, major metabolic disorders, aging, environmental pollutants, drugs, and mycosis) is not a direct cause of cancer, but it creates favorable conditions for the action of specific carcinogenic noxae, such as oncogenic viruses and chemicals. A humoral unspecific blockade of the basal regulatory system was observed in 1,021 patients. The inhibition of the regulatory system was irreversible in 369 cases: 258 cases of chronic inflammation (autoaggressive diseases, toxoplasmosis, late stages of tuberculosis, chronic progressive multiple sclerosis) and 111 cases of malignant tumor. (25 refs)

- 78-1712 **Trophism of Proliferating Cells and Tumor Growth.** (Rus) Kononenko, A. M. (Central Scientific Res. Roentgenoradiologic Inst., Leningrad, USSR); Gordeladze, A. S.; Kovaleva, I. P. *Vestn Akad Med Nauk Ssr* (1): 71-75; 1978.

A fundamental thermodynamic principle, ie, that acceleration of the processes in an open system leads to loss of its regulation, was applied to a population of proliferating tumor cells. It was assumed that the intensity of the ingoing flow of substances and, thus, the increment in the mass of the cells due to their proliferation would be directly correlated with the product of av cell volume(s) and av mitotic index (I). This index (Is) was assessed in five biopsy specimens of human esophageal carcinoma. The minimal values of Is were recorded in normal esophageal epithelium and hyperplastic epithelial cells. The Is values were 8 - 10 times greater in squamous cell keratinizing invasive tumors and carcinomas in situ than in normal epithelium, but they were only 4 times greater in

squamous cell nonkeratinizing carcinomas in situ than in normal epithelium. (8 refs.)

- 78-1713 **10 nM Filaments in Normal and Transformed Cells.** (Eng) Hynes, R. O. (Center Cancer Res Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Destree, A. T. *Cell* 13(1): 151-163; 1978.

An antibody was raised against an electrophoretically homogeneous protein [mol wt of 58,000 daltons (58K)] from cultured NIL8 hamster fibroblasts and used to study the distribution of 58K protein fibrils in cells under a variety of conditions. The antiserum stained an array of cellular filaments that were distinct from microtubules or microfilaments and that were identified as 10-nm filaments. Evidence for this was derived from correlation of the behavior, in colchicine-treated cells, of the filament bundles observed by immunofluorescence with that of the 10-nm filament bundles observed by electron microscopy. The filaments were polymerized at all times and were not disrupted by nonionic detergents or cytochalasin B. The distribution of the filaments was altered by colchicine, which disrupts the microtubules. Colchicine treatment of NIL8 cells transformed with hamster sarcoma virus caused the filaments to retract into a juxtanuclear coil, but it caused filaments from normal cells to form a circumnuclear ring plus a cytoplasmic coil. Thus, although the 10-nm filaments are not disrupted on transformation, their organization or interaction with other components is altered. (50 refs)

- 78-1714 **Origin and Evolution of Benign Prostatic Enlargement.** (Eng) McNeal, J. E. (Herbert A. Harman Memorial Hosp., Berkeley, CA, 94704). *Invest Urol* 15(3): 340-345; 1978.

Benign prostatic enlargement was analyzed quantitatively in 63 autopsy prostates. The 57 prostates that contained nodules were mapped to identify the precise area in which the very small, early nodules arose. The nodules were found to have originated selectively from a very small region, near a cylindrical urethral sphincter above the verumontanum. Most nodules arose from the glands and stroma of the transitional zone, a small wedge of tissue lying immediately lateral to the lower end of the sphincter and partially mingling with the fibers of its outer half. Nodules originated through eccentric budding toward a focus, suggesting local stromal inductive effects. Benign prostatic enlargement evolved through three processes: early diffuse gland growth, small nodule proliferation, and later nodule enlargement. If these processes are



pendent, the etiology of benign prostatic enlargement may be multifactorial. It is possible that only later nodule enlargement, which occurs around 70 yr of age, may be under endocrine control, and the hormone involved may be one that has not yet been investigated in connection with this disease. (16 refs)

78-1715 **Malignancy Arising in Extragonadal Endometriosis. A Case Report and Summary of the World Literature.** (Eng) Brooks, J. J. (Box 303, Hosp. Univ. Pennsylvania, Philadelphia, PA 19104); Wheeler, J. E. *Cancer* 40(6): 3065-3073; 1977.

The case report of a 48-yr-old nulliparous woman with papillary adenocarcinoma arising in extragonadal endometriosis is presented. Four years previously, she had undergone supracervical hysterectomy and bilateral salpingophorectomy. Pelvic endometriosis and multiple abdominal adhesions were encountered; multiple leiomyomas were present in the uterus. She was then treated with 1.25 mg/day of progesterone therapy (3 wk on, 1 wk off) for 4 yr. The adenocarcinoma was predominantly a clear cell type and was no more than 2 mm from the closest focus of endometriosis. The patient is without evidence of tumor 22 mo after surgery. A review of the literature indicated that most malignancies arising in extragonadal endometriosis are adenocarcinomas in nulliparous and perimenopausal patients. Prognosis appeared to be affected by site and histologic type. (81 refs.)

78-1716 **Endocrine-Biochemical Analyses in Precancer of the Vulva.** (Rus) Krivets, N. A. (Kazakh Scientific Res. Inst. Oncology and Radiology, Alma-Ata, USSR); Karimova, T. A.; Subetto, E. I.; Togaibaeva, Z. I. *Russk Ginekolog (Mosk)* (9): 41-43; 1977.

The functional state of the liver and estrogen and androgen secretion and DNA content in the vulval tissue were studied in 75 patients with precancer (leukoplakia) of the vulva. The patients could be divided into two groups: (1) women with 5-yr duration of menopause and (2) women who were in menopause for > 10 yr. In all patients, the content of total proteins and albumin and globulin fractions was within the normal range. They had significantly increased hepatic aspartate aminotransferase activity [41.3 units (u) vs 26.0 u in healthy controls] and alanine aminotransferase activity (39.7 vs 25.7 u in controls). Group 1 patients had slightly decreased excretion of total estrogens (6.0 mg/day vs 7.8 mg/day in controls) and slightly increased excretion of 11-oxy-17-ketosteroids (1.58 µg/day vs 1.24 µg/day in controls), but the Group 2 patients had increased excretion of both estrogens (8.4 mg/day vs 4.4 mg/day in controls) and 11-oxy-17-ketosteroids (1.17 µg/day vs 0.39 µg/day in controls). The average DNA content per nucleus in the vulval cells was increased from 7.0 in healthy controls to 8.3 u in the patients. (6 refs.)

78-1717 **Early Squamous Cell Carcinoma of the Uterine Cervix. III. Frequency of Lymph Node Metastases.** (Eng) Lohe, K. J. (Dept. Obstetrics and Gynecology, Univ. Munich, 8000 Munich 2, W. Germany). *Gynecol Oncol* 6(1): 51-59; 1978.

The frequency of lymph node metastases occurring in early cervical cancer (ECC) was determined. Frequencies reported in the literature range from 0.1% to 10%; however, single case reports are quoted many times and by several authors, creating the impression that lymph node metastases are not uncommon. A review of the 34 published cases of lymph node metastases in ECC or microcarcinoma shows that the dimensions of 26 tumors exceed the limits of early stromal invasion and microcarcinoma defined by the authors. Four other cases were poorly documented. As a result, only 4/34 cases of microcarcinoma with lymph node metastases may actually be regarded as such. Examination of the frequency of histologically proved lymph node metastases in published cases of surgically treated (lymphadenectomy) ECC showed that after deduction of the three Stage IB cases in metastases, metastatic invasion of the pelvic lymph nodes occurred in only 2/605 patients (0.3%). In every case, the involved nodes were located on the pelvic wall and never in the parametrium. (55 refs)

78-1718 **Role of Myo-Epithelial Cells in Breast Carcinoma (Meeting Abstract).** (Eng) Ghosh, L. (Univ. Illinois at the Abraham Lincoln Sch. Medicine and Cook County Hosp., Chicago, IL, 60612); Ghosh, B. C.; Das Gupta, T. K. *Proc Am Assoc Cancer Res* 19: 5; 1978. (no refs)

78-1719 **Stereo Observations on Mechanism of Early Invasion in Human Breast Cancer Using High Voltage Electron Microscope (HVEM) (Meeting Abstract).** (Eng) Whaley, D. A. (State Univ. New York at Buffalo, Buffalo, NY, 14226); Parsons, D. F. *Proc Am Assoc Cancer Res* 19: 143; 1978. (no refs)

78-1720 **Mammary Tumors, Hepatocellular Carcinomas, and Pancreatic Islet Changes in C3H-Avvy Mice.** (Eng) Sass, B. (Registry Experimental Cancers, Del Ray Building, NCI, NIH, Public Health Service, U.S. Dept. Health, Education and Welfare, Bethesda, MD 20014); Vernon, M. L.; Peters, R. L.; Kelloff, G. J. *J Natl Cancer Inst* 60(3): 611-621; 1978.

A total of 187 C3H-Avvy mice were studied for tumor development during their natural life-spans. Hepatocellular carcinomas occurred in 54.3% of males, mammary carcinomas in 95% of females, pancreatic islet cell adenomas in 9.4% of males and in no females, and pancreatic islet cell hyperplasia



in 41% of males and 23% of females. Islet cell hyperplasia and adenomas appeared to consist predominantly of alpha and delta cells. Multiple tumors and/or hyperplasia of a single site or of multiple sites occurred as frequently in males as in females (49.6% and 51.7%, respectively). The most frequent neoplasms were hepatocellular carcinomas and islet cell tumors or hyperplasia in males (45.7%) and multiple mammary tumors in females (30%). Intracytoplasmic A particles were associated with B-type particles in the mammary tumors; however, intracisternal A particles were significantly more frequent in males than in females. The previously unreported tumors found in the mouse strain included 12 islet cell adenomas, 2 spindle cell tumors of the meninges and olfactory lobes, a squamous cell carcinoma of the nasal turbinates, and a schwannoma of the spermatic cord. (15 refs.)

- 78-1721 Malignant Papillomatosis of the Intrahepatic Bile Ducts.** (Eng) Helpap, B. (Inst. Pathology, Univ. Bonn, Postfach 2120, D-5300 Bonn-Venusberg, W. Germany). *Acta Hepatogastroenterol* 24(6): 419-425; 1977.

A 41-yr-old woman developed a mucin-secreting papillary adenocarcinoma after several recurrent episodes of intrahepatic bile duct papillomatosis. No bile duct concretions were evident. It is suggested that this type of tumor could arise from chronic irritation due to concretions, congenital anomalies, developmental disturbances, or disturbances in bile and cholesterol metabolism. (40 refs)

- 78-1722 The Histogenesis of Hepatoma Occurring Spontaneously in a Strain of Sand Rats (*Psammomys obesus*).** (Eng) Ungar, H. (Dept. Pathology, Hadassah Medical Sch., P. O. Box 1172, Jerusalem, Israel); Adler, J. H. *Am J Pathol* 90(2): 399-410; 1978.

A systematic histologic study was performed on the liver of sand rats (*Psammomys obesus*) ranging in age from weanlings to 38 mo (the expected life-span) and taken from two colonies in which spontaneous hepatomas and hepatic preneoplastic changes had been observed. Starting at 6 mo and increasing with increasing age, nodules containing hepatocytes characterized by hyperbasophilia, glycogen deposits, eosinophilic cytoplasm, or a mixture of these cells were found. Hepatocellular carcinoma was diagnosed in rats > 25 mo old. These changes were found in livers free of cirrhosis and inflammatory lesions. Malignant changes developed only from nodules, never from hyperplasia; the tumors invaded the hepatic veins, but no distant metastases were found. These patterns of cellular and histologic changes have, until now, been reported only in connection with chemically induced carcinogenesis in rats. However, external chemical carcinogen could be demonstrated in the animal colonies, and a hereditary predisposition to tumor formation is presumed. (19 refs)

- 78-1723 Hepatosplenic Angiosarcoma. Report of a Case and Review of the Literature.** (Fre) Libeskind, M. (Service de Gastroenterologie, Centre Hospitalier de Gonesse, F 95500 Gonesse, France); Lugagne, F.; Malbran, J.; Villemant, J. F.; Guyet-Rousset, P. *Gastroenterol Clin Biol* 1(12): 1027-1034; 1977.

Primary angiosarcomas of the liver and spleen were diagnosed in a 37-yr-old man who had never been exposed to vinyl chloride. (28 refs)

- 78-1724 Studies on Mucopolysaccharide Metabolism in Juvenile Angiofibroma.** (Ger) Kuttner, H. (Hals-Nasen-Ohrenklinik, Friedrich-Schiller-Universität, Lessingstrasse 2, DDR-69 Jena, E. Germany); Katenkamp, D.; Stiller, D. *Arch Otorhinolaryngol* 218(1/2): 45-59; 1977.

The mucopolysaccharide (glucosaminoglycan) metabolism in juvenile nasopharyngeal angiofibroma was studied histologically, chemically in 10 tumors and ultrahistochemically in 4. The endothelium of the vessels exhibited a strong PAS reaction and acid groups on the cell surface. The interstitial tissue showed a mild PAS reaction and contained acid mucopolysaccharides located near the fibrillar structures. Electron microscopically, the PAS-positive material was located in the cytoplasm of typical fibroblast and histiocyte-like fibroblasts. The acid groups of the carboxylated and sulfated mucopolysaccharides of the intercellular substance were identified as hyaluronic acid and chondroitin-4 and chondroitin-6 sulfates by the critical-electrolyte-concentration method. Ultrastructurally, these acid groups coated the fibroblast membranes and occurred within the cell between the collagen fibrils. The findings indicate the regular differentiation of the cell-surface structure and support the hypothesis of an organoid growth pattern of juvenile angiofibroma. (38 refs)

- 78-1725 Pathogenesis of the Lewis Lung Carcinoma: Invasion and Destruction of Host Muscle and Lung (Meeting Abstract).** (Eng) Newton, P. (Depts. Zoology and Radiation Therapy, Howard Univ., Washington, D. C. 20059); Choppala, J.; Henschke, U. *Proc Am Assoc Cancer Res* 19: 170; 1978. (no refs)

- 78-1726 Human Lung Carcinoma Lines in Culture and in Athymic Nude Mice (Meeting Abstract).** (Eng) Sharkey, F. E. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033); Hajdu, S.; Fogh, J. *Fed Proc* 37(3): 596; 1978. (no refs)



1727 **The Relationship of Laryngeal Keratosis and Subsequent Carcinoma (Meeting Abstract).** (Eng) Crissman, J. D. (Dept. Pathology, Univ. Cincinnati Medical Center, 234 Goodman St., Cincinnati, OH, 45267); W. Y. *Am J Clin Pathol* 69(2): 212-213; 1978. (no refs)

1728 **Fine Structural Observations of Oral Squamous Cell Carcinoma (Meeting Abstract).** (Eng) Zaki, L. (Coll. Dentistry and Medicine, Univ. Illinois, Chicago, El-Domeiri, A. A. *J Dent Res* 57(A): 261; 1978. (no refs)

1729 **Intraoral Basal Cell Carcinoma.** (Eng) Samit, A. M. (Oral Surgery Section, Veterans Admin. p., East Orange, NJ, 07019). *J Surg Oncol* 10(1): 27-32; 1978. (no refs)

A 4-yr-old man was diagnosed as having a basal squamous carcinoma of the oral mucosa, and the lesion was treated with surgery. The lesion recurred 7 yr later and was treated with radiotherapy. Since the initial complaint, the history and course of the lesion, and the microscopic findings are consistent with previously reported cases of basal cell carcinoma of the mucous membrane, it is suggested that the original diagnosis was incorrect. (19 refs)

1730 **Malignant Fibrous Histiocytoma. An Ultrastructural Study of Six Cases.** (Eng) Alguacil, A. (Section Publications, Mayo Clinic, 200 First St. Rochester, MN, 55901); Unni, K. K.; Goellner, J. R. *J Clin Pathol* 69(2): 121-129; 1978.

The ultrastructure of six malignant fibrous histiocytomas was studied. Four of the tumors arose in the soft tissues of the thigh, one in the retroperitoneum, and one in the greater omentum. The lesions were composed of fibroblastic- and histiocytic-appearing cells, with the fibroblastic-appearing cells being predominant in all lesions. Intermediate, undifferentiated, and foam cells were also present. Three of the tumors had some fibroblasts that had intracytoplasmic bundles of filaments with focal densities (myofibroblastic cells). These findings suggest that malignant fibrous histiocytoma is a mesenchymal sarcoma with an undifferentiated mesenchymal cell origin, differentiating along a broad fibrohistiocytic spectrum, with most of the cells showing variants of myofibroblastic differentiation. (46 refs)

1731 **Multiple Childhood Osteosarcomas in an American Indian Family with Erythroid Mac-**

rocytosis and Skeletal Anomalies. (Eng) Mulvihill, J. J. (Clinical Genetics Section, Clinical Epidemiology Branch, Landow Building, Room A521, NCI, Bethesda, MD 20014); Gralnick, H. R.; Whang-Peng, J.; Leventhal, B. G. *Cancer* 40(6): 3115-3122; 1977.

The development of osteosarcoma, limb anomaly, and erythroid macrocytosis in a 15-yr-old girl, following the death of a brother and a sister from osteosarcoma, prompted genealogical and laboratory investigations of the family. Two months after the proband diagnosis, a 19-yr-old sister developed a fibroadenoma of the right breast. Genealogy revealed that the American Indian (full-blooded Oneida) parents were possibly consanguineous; they had a total of nine children. Limb anomalies and elevated mean corpuscular volumes were detected in the proband, several sibs, and her father. Limb anomalies included simple clinodactyly with brachymesophalangy, the absence of one digital ray of the foot, and bilateral radioulnar synostosis. The erythroid macrocytosis was not accompanied by anemia, and it could not be explained by the usual causes. There were no unusual environmental exposures, and no oncogenic viruses were detected. All family members had elevated antibody titers to Epstein-Barr viral antigens. The proband and her father had excessive chromosomal breaks in the bone marrow. This syndrome has been named OSLAM (osteosarcoma, limb anomalies, and erythroid macrocytosis with megaloblastic marrow), and it may represent impaired regulation of bone development. (47 refs.)

78-1732 **Complicated Polymyalgia (2 Letters to Editor).** (Eng) Bruckner, F. (Dept. Rheumatology, St. George's Hosp., London SW1, England); Hackett, P. J. *Br Med J* 1(6107): 235-236; 1978.

Three additional cases further support the reported association of polymyalgia rheumatica (PR) or temporal arteritis with malignancy. The poor response of PR to corticosteroids indicates the possibility of an occult neoplasm. Therefore, PR, like polymyositis, should be regarded as a marker of malignancy. (no refs)

78-1733 **Aetiology of Adenoma-Carcinoma Sequence in Large Bowel.** (Eng) Hill, M. J. (Central Public Health Lab., Colindale, England); Morson, B. C.; Bussey, H. J. *Lancet* 1(8058): 245-247; 1978.

A hypothesis for the etiology of adenoma-carcinoma sequence in large bowel neoplasms is proposed based on the results of previous studies. In populations with a low incidence of colorectal cancer, the incidence of adenomas varies greatly. Furthermore, the subsite distribution of adenomas within the colon and rectum differs from that of carcinomas.



Thus, if all cancers arise in adenomas, the agent causing adenomas differs from that causing the malignant change; ie, more than one agent is involved in the etiology of colorectal cancer. Large adenomas have a greater malignant potential than small adenomas. The subsite distribution and incidence of large adenomas approximate those of colorectal cancer. Thus, the major factor in determining carcinoma incidence is the one that causes adenomas to grow to a large size, rather than the one that actually causes malignant change. A genetic predisposition to adenomas has been proposed, with a recessive gene making a person adenoma-prone. It is suggested that environmental agent A, which causes adenomas, will act in adenoma-prone cells to create small adenomas. These adenomas would then be stimulated either by environmental agent B, which causes the adenomas to grow, and/or agent C, which causes the adenomas to develop into carcinomas. It is suggested that the agent causing the adenomas to grow is a bacterial metabolite of the bile acids already incriminated in the etiology of large-bowel cancer. (28 refs)

- 78-1734 Management of Malignancy in "Cancer Families".** (Eng) Williams, C. (Medical Oncology Unit, Centre Block, CF93, Tremona Road, Southampton General Hospital, Southampton SO94XY, England). *Lancet* 1(8057): 198-199; 1978.

A 36-yr-old woman presented with a primary carcinoma of the colon 14 yr after removal of a ceceal adenocarcinoma and 2 yr after removal of two primary colonic adenocarcinomas with metastatic involvement of both ovaries. The tumor recurrences in this individual prompted the taking of a thorough family history. The study revealed that she was a member of a cancer family: of 44 members traced through four generations, 16 had cancer (5 had multiple cancers). The age at tumor onset tended to be earlier in these subjects than that expected in a normal population. There was a wide range of tumors, although colonic and uterine cancers were the most common. The pattern of inheritance of susceptibility to cancer is compatible with an autosomal dominant mechanism. Members of these families should be screened routinely for development of malignancy. (23 refs)

- 78-1735 Cancer (Ca) Incidence in Membranous Nephropathy (MN) (Meeting Abstract).** (Eng) Yamauchi, H. (Univ. California, San Francisco, CA); Biava, C. G.; Lee, J. C.; Hopper, J. *Kidney Int* 12(6): 476; 1977. (no refs)

- 78-1736 Familial Renal Cell Carcinoma Associated with A Constitutional Chromosome Translocation: Biological and Clinical Implications (Meeting Abstract).**

(Eng) Li, F. P. (NCI, Bethesda, MD, 20014); Marchetto, D. J.; Cohen, A. J. *Proc Am Assoc Cancer Res* 19: 384; 1978. (no refs)

- 78-1737 Genealogy of Cancer in a Family (Meeting Abstract).** (Eng) Blattner, W. A. (NIH, Bethesda, MD, 20014); McGuire, D. B.; Mulvihill, J. J.; Fraumeni, J. F.; Lampkin, B. C.; Hananian, J. *Proc Am Assoc Cancer Res* 19: 404; 1978. (no refs)

- 78-1738 Nonrandom Chromosome Changes in Human Neoplasia (Meeting Abstract).** (Eng) Mitelman, F. (Dept. Clinical Genetics, Univ. Lund, Lund, Sweden); Levan, G. *Clin Genet* 13(1): 129; 1978. (no refs)

- 78-1739 Genetical Investigations in Familial Hodgkin's Disease (Meeting Abstract).** (Eng) Marshall, W. H. (Clinical Res. Centre, Harrow, England). *Clin Sci Mol Med* 54(2): 21; 1978. (no refs)

- 78-1740 Is Acute Myeloid Leukaemia a Genetic Disease? (Meeting Abstract).** (Eng) Harris, R. (Dept. Medical Genetics, St. Mary's Hosp., Manchester, England); Zuhrie, S. R. *Clin Genet* 13(1): 120; 1978. (no refs)

- 78-1741 Gut Lymphoma Presenting Simultaneously in Two Siblings.** (Eng) Freedlander, E. (Victoria Infirmary, Glasgow G42 9TY, England); Kissen, L. H.; McVie, J. G. *Br Med J* 1(6105): 80-81; 1978.

A 51-yr-old woman and her 54-yr-old brother presented simultaneously with primary intestinal lymphoma, a diffuse small cell type and a mixed small and large cell type, respectively. There was no remarkable family history and the siblings had not lived in the same house for many years. However, both patients had significant IgG titers to Epstein-Barr virus; the significance of this finding is unknown. (5 refs)

- 78-1742 Burkitt's Lymphoma (Meeting Abstract).** (Spa) Callis Nadal, M. (Hospitalet Llobregat, Barcelona, Spain); Romagosa Puig, V.; Canadas Sauras, F.; Domingo Claros, A.; Milla Santos, F.; Clavo Sebastian, M.; Ferran Camps, C. *Sangre (Barc)* 23(1): 109-110; 1978. (no refs)



8-1743 **Qualitative Platelet Defects in Preleukemia (Meeting Abstract).** (Eng) Rahman, F. (Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 76903); Brown, C. H. *Proc Am Assoc Cancer Res* 19: 309; 1978. (1 ref)

8-1744 **Spontaneous and Induced Preleukemia Cells in C57BL/6 Mice: Brief Communication.** (Eng) Aran-Ghera, N. (Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel). *J Natl Cancer Inst* 60(3): 707-710; 1978.

The occurrence of spontaneous and induced preleukemia cells in C57BL/6 mice was investigated by a transplantation bioassay. The donor mice were treated with either of two radiation-induced leukemia virus variants (D-RadLV or A-RadLV), 7,12-dimethylbenz[a]anthracene (1 mg/wk intragastrically, x 5) or 170 whole-body irradiation (4 weekly doses of 170 rads). Recipient mice were then inoculated with bone marrow, thymus, or spleen cells. Preleukemia cells were identified mainly among the bone marrow cells of old C57BL/6 mice or within 10-30 days after the leukemogenic treatment of young mice. However, in mice treated with A-RadLV, the thymus was the first site to harbor preleukemia cells of donor origin (35%-50% within 10-20 days). All leukemias did not develop until several months later. The effect of thymectomy on the induction of these preleukemic cells was also investigated. This treatment affected viral transformation, but it had no effect on the number of chemical/or x-ray-induced cells. It is suggested that two stages are involved in the long latent period in leukemogenesis: preleukemic transformation and the differentiation and proliferation of preleukemic cells to overt disease. (10 refs)

8-1745 **Multiple Incidence of Thymic Lymphoblastic Lymphoma in a Family with Neurofibromatosis (Meeting Abstract).** (Eng) Cushing, B. (Dept. Pediatrics, Michigan Wayne State Univ. Sch. Medicine, Detroit, MI, 48201); Kaplan, J.; Bhaya, N.; Roskamp, J. *Proc Am Assoc Cancer Res* 19: 362; 1978. (no refs)

8-1746 **Carcinoid Tumour of Possible Thymic Origin: Case Report.** (Eng) Rao, U. (Dept. Pathology, Roswell Park Memorial Inst., 666 Elm St, Buffalo, NY, 14263); Takita, H. *Thorax* 32(6): 771-776; 1977.

The case report of a 48-yr-old man with a carcinoid tumor

of the mediastinum is presented. Since there was no involvement of the bronchi, lungs, or gastrointestinal tract, it was suggested that the carcinoid was a primary tumor, probably of thymic origin. It could have arisen from Kultschitsky cell nests within the thymus. (15 refs.)

78-1747 **Carcinoid Tumour of the Thymus: A Case Report Including Discussion of the Morphological Diagnosis and the Cell of Origin.** (Eng) Chalk, S. (Dept. Pathology, Prince Charles Hosp., Chermside, Queensland 4032, Australia); Donald, K. J. *Virchow Arch [Pathol Anat]* 377(1): 91-96; 1977.

The case history is presented of a 49-yr-old asymptomatic man who had a mediastinal mass demonstrated on routine radiography. A large encapsulated carcinoid tumor of the thymus was excised. Light microscopy showed that it was composed of small regular cells arranged in clumps and acini with fine vascular stroma. Thymic tissue was present within the capsule and vascular and capsular invasion was seen. The histology of the tumor is presented with emphasis on the difficulties involved in the differential diagnosis of the lesion. (13 refs)

78-1748 **A Case of Colloid Cyst of the Third Ventricle: Anatomoclinical and Histogenetic Consideration.** (Ita) Zanetti, G. (Istituto di Anatomia e Istologia Patologica, Università di Bologna, Bologna, Italy); Gordini, G. *Pathologica* 69(995/996): 529-535; 1977.

A colloid cyst of the third ventricle was found in a 38-yr-old woman. The cyst contained mucopolysaccharides secreted by the parietal cells, and it appeared to have originated from the primitive neuroepithelium, with possible involvement of the paraphysis. (25 refs)

78-1749 **Increasing Incidence of Brain Metastases in Sarcoma Patients. (Meeting Abstract).** (Eng) Espana, P. (Baltimore Cancer Res. Center, DCT, NCI, Baltimore, MD, 21201); Chang, P.; Wiernik, P. H. *Proc Am Assoc Cancer Res* 19: 370; 1978. (no refs)

78-1750 **Mitosis in the Nontumorous Parts of the Retina with Retinoblastoma.** (Eng) Nakao, F. (Dept.



Ophthalmology, Chihaya Hosp., 1-65, Chihaya Higashi-ku, Fukuoka 813, Japan). *Ophthalmologica* 176(1): 27-33; 1978.

The nontumorous part of the retina from a 2-mo-old girl with a retinoblastoma of the posterior pole was examined by electron microscopy. Mitotic cells were observed in the outer and inner nuclear layers. These cells, which were separated from the tumor mass by 450-600  $\mu$ m, had the ultrastructural features of immature Muller cells. The existence of dividing cells in the posterior retina after birth indicated immaturity of retinal development. (11 refs)

**78-1751 Metastatic Behavior of Human Tumors Growing in Athymic Mice (Meeting Abstract).** (Eng) Kyriazis, A. P. (Univ. Cincinnati Medical Center, Cincinnati, OH, 45267); Pesce, A. J.; DiPersio, L.; Stinnett, D.; Michael, J. G. *Fed Proc* 37(3): 680; 1978. (no refs)

See also:

\*(Rev.): 78-1208, 78-1224, 78-1236, 78-1237, 78-1244, 78-1246, 78-1248, 78-1257, 78-1263, 78-1264, 78-1265, 78-1268.

\*(Chem.): 78-1287, 78-1289, 78-1297, 78-1305, 78-1310, 78-1315, 78-1327, 78-1328, 78-1329, 78-1343, 78-1349, 78-1353, 78-1375, 78-1395, 78-1399, 78-1413, 78-1421, 78-1422, 78-1448, 78-1454, 78-1455, 78-1469, 78-1471, 78-1473, 78-1478, 78-1490, 78-1494, 78-1499, 78-1502, 78-1507, 78-1516.

\*(Phys.): 78-1521, 78-1523, 78-1524, 78-1528, 78-1533, 78-1534, 78-1542, 78-1544, 78-1553.

\*(Viral): 78-1565, 78-1588, 78-1609, 78-1617, 78-1638, 78-1647, 78-1654, 78-1655, 78-1664.

\*(Immun.): 78-1690, 78-1694, 78-1696.

\*(Epid.-Biom.): 78-1754, 78-1766, 78-1767.



## EPIDEMIOLOGY AND BIOMETRY

8-1752 **Application of the Grid Square Method to the Geographical Distribution of Mortality Statistics. I. Geographical Distribution of Cancer Mortality in Tokyo.** (Jpn) Okubo, T. (Dept. Preventive Medicine and Public Health, Keio Univ. Sch. Medicine, Tokyo, Japan); Adachi, S.; Toyama, T. *Jpn J Hyg* 32(4): 534-542; 1977.

The grid square method was used to determine the geographical distribution of cancer mortality in Tokyo. A grid area of approx 1 kilometer<sup>2</sup> was found to be most suitable. When mortality statistics were sparse, four to nine of these areas were summed. Death rates from stomach cancer were highest in northeastern Tokyo, but those from lung cancer were highest in the southwestern area of the city. (5 refs.)

8-1753 **Cancer Incidence and Mortality Trends in the United States: 1935-1974.** (Eng) Devesa, S. S. Biometry Branch, NCI, NIH, Public Health Service, U. S. Dept. Health, Education, and Welfare, Bethesda, MD, 20814; Silverman, D. T. *J Natl Cancer Inst* 60(3): 545-571; 1978.

Incidence data from three national cancer surveys and nationwide mortality data indicate that cancer rates are increasing among men and decreasing among women. White predominance has been replaced by a nonwhite excess in incidence and mortality rates among men and a nonwhite excess in female mortality. Without lung cancer, the incidence of cancer types combined would be decreasing among white men. Increases in overall incidence among nonwhite men are due primarily to increases in lung, prostatic, intestinal, and esophageal cancers. Among women, the decreased overall incidence is due to decreases in uterine cervix and stomach cancers; breast cancer rates are steady, and they continue to have a major impact. Except for breast cancer, the experience of nonwhite women is similar, with declines in uterine cancer being greater and those at other sites being less than the declines occurring in white women. (20 refs.)

8-1754 **Nasopharyngeal Cancer in Greenland. The Incidence in an Arctic Eskimo Population.** (Eng) Mikkelsen, N. H. (Univ. Inst. Forensic Medicine, Frederik V's Vej 11, DK-2100 Copenhagen O, Denmark); Mikkelsen, F.; Hansen, J. P. *Acta Pathol Microbiol Scand [A]* 85(6): 850-858; 1977.

In the period 1955-1976, 35 cases of nasopharyngeal cancer

were diagnosed among native Greenlanders, an Eskimo population with some Caucasian blood. The patients (20 men and 15 women) ranged in age from 21 to 74 yr. Thirty-three tumors were squamous cell carcinomas, including 20 lymphoepitheliomas, and 2 were malignant lymphomas. Age-adjusted incidence rates for 1965-1976 were 12.3 and 8.5/100,000/yr for men and women, respectively. These rates are among the highest in the world, and they are significantly higher than those in Denmark. An additional 11 patients with secondary tumors of the cervical lymph nodes may have had an undiagnosed primary nasopharyngeal cancer. Thus, the calculated incidence rates could be minimum rates only. Further studies are needed to clarify the histocompatibility antigen and serologic Epstein-Barr virus profiles of Greenlanders. (42 refs)

78-1755 **Epidemiology of Lung Cancer.** (Ger) Berndt, H. (Klinik für Innere Medizin, Bezirkskrankenhaus, Wilhelm-Kulz-Strasse, DDR-20 Neubrandenburg, E. Germany). *Z Erkr Atmungsorgane* 148(2): 163-178; 1977.

The epidemiology of cancer of the trachea, bronchus, and lung in East Germany is discussed. The annual incidence is approx 7,500 cases, and the annual mortality is nearly 7,000 cases. The age-adjusted incidence increases by about 1% per yr. Regional differences in incidence and mortality are due to environmental factors. The most important etiological factor is inhalation of cigarette smoke; occupational hazards such as asbestos, radioactive dusts, metals, and organic compounds may be dangerous to the exposed population, but the influence on morbidity appears to be moderate. Previous non-specific diseases of the respiratory system and tuberculosis contribute to the increased risk of lung cancer. (92 refs.)

78-1756 **Standards for Environmental Releases from Mining and Milling of Uranium. 1. Exposure to Radon Daughters and the Incidence of Lung Cancer.** (Eng) Ellett, W. H. (Environmental Protection Agency, Washington, DC). In: *Transactions of the American Nuclear Society, 1977 Winter Meeting, Nov. 27-Dec. 2, 1977, San Francisco, CA* pp. 148-149; 1977.

Studies of the association between exposure to radon daughters in uranium and a variety of hard rock mines and lung cancer are considered. Control of radon in US underground uranium mines was slow to develop, so that miners were exposed to relatively large doses in the post-World War II



years. Early epidemiological studies, therefore, do not provide information on the risk at relatively low exposures. In a recent Canadian study, however, the average exposure of those succumbing to lung cancer was 75 working-level months (WLM) compared to 2,000 WLM in a recent US study. Analyses of the Canadian data have indicated that there is a linear relationship between exposure to radon daughters and lung cancer risk and that if a threshold exposure is needed to cause lung cancer, it is  $< 10$  WLM. It is evident that occupational exposure to radon daughters leads to an increased risk of lung cancer and that this risk extends to levels of exposure that are below current occupational guidelines. (5 refs.)

**78-1757 Comparative Epidemiology of Tobacco-related Cancers.** (Eng) Wynder, E. L. (Div. Epidemiology, Naylor Dana Inst. Disease Prevention, American Health Foundation, New York, NY 10019); Stellman, S. D. *Cancer Res* 37(12): 4608-4622; 1977.

In a retrospective study, interviews eliciting information on smoking habits were obtained from 3,716 patients with cancer of the lung (Kreyberg types I and II), mouth, larynx, esophagus, or bladder and  $> 18,000$  controls. For each of these cancers, the relative risk smokers of both sexes increased with the quantity smoked and the duration of the habit. The strongest increase occurred for cancer of the lung and larynx, the least increase for cancer of the esophagus and bladder. For ex-smokers, the risk decreased with years of cessation. The risk for mouth cancer of pipe and cigar smokers, who inhaled much less than cigarette smokers, was less than that of the latter and increased with the quantity smoked. The risk of mouth, larynx, and esophagus cancer among smokers increased with the quantity of alcohol consumed. Greater smoking habits and lesser cessation rates were noted among lower socioeconomic groups, suggesting that these groups will develop an ever-increasing proportion of tobacco-related cancers. (43 refs.)

**78-1758 Geographic and Time Trends of Coffee Imports and Bladder Cancer.** (Eng) Morrison, A. S. (Dept. of Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115). *Eur J Cancer* 14(1): 51-54; 1978.

Bladder cancer incidence rates were related to per capita coffee imports for 10 countries and time trends in these variables were analyzed for the US and Denmark. For the 10 countries (Japan, Norway, East Germany, Finland, Sweden, Canada, Denmark, New Zealand, United Kingdom, US), the age-adjusted annual bladder cancer rate for men increased 0.45/100,000 for each kilogram of coffee imported person per yr; the corresponding figure for women was 0.23. There was a

weak positive correlation between time trends of coffee imports and bladder cancer incidence for men only in the US; in Denmark, there was no correlation between bladder cancer incidence and coffee imports. These results suggest that the previously observed positive associations between coffee and bladder cancer are not the result of a causal link. (15 refs.)

**78-1759 Digestive Tract Tumors in the Cote d'Or Region of France.** (Fre) Faivre, J. (Registre Bourguignon des Cancers Digestifs, Faculte de Medecine, 7, boulevard Jeanne d'Arc, F 21000 Dijon, France); Legoux, J. L.; Faivre, M.; Martin, F.; Klepping, C. *Gastroenterol Clin Biol* 1(12): 983-993; 1977.

Epidemiological data on digestive tract tumors that occurred in the Cote-d'Or region of France (population 455,727) during 1976 are presented. Within the year, 357 deaths and 450 new cases of digestive cancer were recorded. The crude annual incidence rates were 120/100,000 in men and 70/100,000 in women. The new cases included 38 esophageal cancers, 8 stomach cancers, 1 small intestinal cancer, 124 colorectal cancers, 2 anal cancers, 34 liver cancers, 28 pancreatic cancers, 21 bile duct cancers, and 28 cancerous cysts. Esophageal cancer accounted for 42 deaths, stomach cancer for 90, small intestine cancer for 3, colorectal cancer for 204, anal cancer for 5, liver cancer for 32, pancreatic cancer for 39, bile duct cancer for 26, and cancerous cysts for 9. The age-standardized incidence was higher in men than in women except for bile duct cancer. Comparison with other countries showed a medium risk of cancer of the stomach, colon, and pancreas and an increased risk of primary liver and esophageal cancer in this region. (18 refs.)

**78-1760 Cancer of the Large Bowel, Based on Record at the Medical Academy of Cracow for the Years 1957-1976.** (Pol) Papla, B. (Instytutu Patologii, ul. Grzegorzewska 16, 31-531 Krakow, Poland); Urban, A. *Patol Pol* 28(4): 449-468; 1977.

The incidence of large bowel cancer is surveyed based on 1,640 cases seen between 1957 and 1976. The male:female ratio for cancer of the rectum was 1.02, but that for cancer of the colon was 0.88. The mean age for men with rectal cancer was 61.9 yr and that for men with colon cancer was 57.6 yr; the respective figures for women were 60.1 and 59.1 yr. The greatest incidence was in the sixth and seventh decades for both sexes. Localization in the large bowel was similar for both sexes, with women having a slightly higher incidence of cancer of the cecum. Rectal cancer was the most frequent neoplasm, followed by cancer of the sigmoid, ascending and transverse colon, hepatic flexure, splenic flexure and descending colon. For people  $< 49$  yr old, the highest cancer incidence was in the transverse colon, including bot



ures; rectal cancer was less frequent. Most cancers (55%) were adenocarcinomas at various stages of differentiation; there was no difference in incidence by sex. The frequency of mucinous adenocarcinoma ranged from 32.2% in cecum to 5.3% in the rectum. Signet-ring carcinoma and mucinous adenocarcinoma were more common and adenocarcinoma was more rare in younger patients than in older patients. (41 refs)

78-1761 **Colorectal Carcinoma. Epidemiology and Experimental Animal Carcinogenesis.** (Ger) Winkler, R. (Abteilung für Allgemeinchirurgie, Chirurgischen Universitätsklinik Hamburg, Univ.-Krankenhaus Eppendorf, Martinistrasse 52, 2000 Hamburg 20, W. Germany). *Deutsche Med* 96(3): 115-119; 1978.

Epidemiological studies of colorectal carcinoma are discussed. In Hamburg, West Germany, the age-standardized rates for this carcinoma have increased from 14.5 cases/10<sup>5</sup> inhabitants between 1872 and 1896 to 31.0 between 1956 and 1960 and to 40.6 between 1971 and 1974. These changes reflect a changing exposure to environmental carcinogens, and they were most important for distal colonic carcinoma. They have been correlated with changes in diet and working conditions. Data suggest different etiologies for carcinoma of the right colon, left colon, and rectal ampulla. In experimental studies, male Wistar rats received intrarectal infusions of 2 g/kg N-methyl-N'-nitro-N-nitrosoguanidine twice weekly for 7 mo. The frequency and size of the resulting polyps and cancers were significantly reduced in colons excluded from fecal passage by a diverting colostomy. Thus, feces appear to possess co-carcinogenic properties. If the ileum was anastomosed to the distal colon, however, no neoplastic lesions were induced. This suggests that the ileal contents have carcinoprotective properties. Adenocarcinomas with various degrees of differentiation developed in all colostomized rats. It is suggested that these adenocarcinomas arose both from open implantation of that section of the descending colon excluded from fecal passage in the abdominal wall, and by eversion of the mucosa of that section of colon within the abdominal wall. (38 refs)

78-1762 **Colorectal Cancer and Diet in Blacks (Meeting Abstract).** (Eng.) Dales, L. G. (Kaiser Foundation Res. Inst., Oakland, CA 94611); Friedman, G. D.; Ury, J. K.; Williams, S. R.; Grossman, S. *Am J Epidemiol* 106(3): 200, 1977. (no refs.)

78-1763 **Colorectal Carcinoma in Adolescents: Implications Regarding Etiology.** (Eng) Pratt, C. B. (St. Jude Children's Res. Hosp., P. O. Box 318, Memphis, TN

38101); Rivera, G.; Shanks, E.; Johnson, W. W.; Howarth, C.; Terrell, W.; Kumar, A. P. *Cancer [Suppl]* 40(5): 2464-2472; 1977.

Of 13 adolescent patients (6 boys and 7 girls) with advanced, poorly differentiated colorectal carcinoma, 4 were from urban areas and 9 from rural areas. A history of exposure to farm or agricultural chemicals was documented for eight of the rural patients and for one of the urban patients. This group of patients differed from adults with colorectal carcinoma with respect to tumor site (throughout the large intestine), tumor histology (mucin-producing adenocarcinoma), and their poor response to chemotherapy with vincristine, 1-(2-chloroethyl) -3- (trans 4- methylcyclohexyl) -1-nitrosourea, and 5-fluorouracil. Only two patients showed a measurable response, and 4/5 still living have evidence of active disease at up to 26 mo after diagnosis. Although dietary factors have been implicated in adult colorectal carcinoma, these results suggest that alternate etiologies must be considered for the disease in adolescents or children. (67 refs.)

78-1764 **Relationship Between Diet and Carcinoma of the Stomach, Colon, Rectum, and Pancreas in France.** (Fre) Meyer, F. (Unité de Recherche de Physiopathologie Digestive, INSERM U-45, Hôpital E.-Herriot, Pavillon H, F 69374 Lyon Cedex 2, France). *Gastroenterol Clin Biol* 1(12): 971-982; 1977.

An investigation was made to determine if there were any correlations between the consumption of 13 food items (bread, potatoes, fresh vegetables, fresh fruits, beef, eggs, fish, cheese, butter, oil, sugar, wine, and beer) and the age-standardized mortality rates for carcinomas of the stomach, colon, rectum, and pancreas in eight districts of France. Significant correlations ( $p \leq 0.05$ , correlation coefficient  $> 0.66$ ) were found between potato consumption and colon cancer (+0.68), rectal cancer (+0.82), and pancreatic cancer (+0.67); fruit consumption and stomach cancer (-0.66), colon cancer (-0.83), and rectal cancer (-0.77); butter consumption and colon cancer (+0.74); oil consumption and stomach cancer (-0.72), colon cancer (-0.83), and rectal cancer (-0.71); wine consumption and pancreatic cancer (-0.69), and beer consumption and cancer of the rectum (+0.73) and pancreas (+0.73). The findings suggest that the consumption of saturated fatty acids facilitates the development of colon cancer. (31 refs)

78-1765 **Sociocultural Factors Associated with Cervical Cancer in Bendel State, Nigeria.** (Eng) Emovon, A. C. (Centre Social, Cultural and Environmental Studies, Univ. Benin, Private Mail Bag 1154, Benin City, Nigeria). *Int J Gynaecol Obstet* 15(3): 253-255; 1977.



Of 15,049 gynecologic patients seen at a Nigerian hospital between March 1973 and December 1976, 65 had cervical cancer. Data collected from 50 of the cancer patients in questionnaire interviews showed that 80% had no formal education and that the majority came from lower socioeconomic groups. Most of the patients (88%) had married before age 20, and 76% reported frequent coitus. Their parity pattern (para 1-5) was similar to that of the general population. The low incidence of cervical cancer in this series may be due to the fact that Nigerian men are circumcised in infancy. (8 refs.)

**78-1766 Dysplasias of Uterine Cervix. Epidemiological Aspects: Role of Age at First Coitus and Use of Oral Contraceptives.** (Eng) Meisels, A. (1050, Chemin Ste-Foy, Quebec, Province Quebec, Canada G1S 4L8); Begin, R.; Schneider, V. *Cancer* 40(6): 3076-3081; 1977.

The relationship among age at first coitus, use of oral contraceptives, and dysplasia of the uterine cervix was investigated in a 95% homogeneous population of French Canadian women. Of 153,231 patients screened for the first time between 1972 and 1975, 3,463 had dysplasia; the prevalence of dysplasia remained at essentially the same high rate between ages 15 and 44 yr. The use of oral contraceptives was known in 92.5% of the dysplasia patients, age at first coitus in 59.8%, and both factors in 59.8%; the respective figures for the entire population of newly screened patients were 93.7%, 56.9%, and 55.2%. Highly significant correlations were found between early onset of sexual activity and dysplasia, oral contraceptive use and dysplasia, and early age at first coitus and oral contraceptive use. When corrections were made for age at first coitus, there was a significant excess of dysplasias in the oral contraceptive group. Two types of dysplasia may exist: one regressing spontaneously and one progressing to carcinoma in situ and invasive cancer. The excess of dysplasia in oral contraceptive users must be explained before it can be stated that the use of these drugs does not increase the risk of cervical cancer. (20 refs.)

**78-1767 Influence of Age at First Pregnancy on Breast Parenchymal Pattern: A Preliminary Report.** (Eng) Andersson, I. (Dept. Diagnostic Radiology, Malmo General Hosp., Univ. Lund, S-214 01 Malmo, Sweden); Andren, L.; Pettersson, H. *Radiology* 126(3): 675-676; 1978.

The breast parenchymal patterns of 1,300 randomly selected women (aged 50-60 yr) were determined and related to age at first pregnancy. There was a higher number of low-cancer-risk parenchymal patterns for women first parous before age 20; there was a higher number of high-cancer-risk parenchymal patterns for women first parous after age 32 and in nul-

liparous persons. These findings support the hypothesis of a relationship between breast parenchymal pattern and cancer risk. (8 refs)

**78-1768 Malignant Breast Tumors--Epidemiological Characteristics in Towns and Villages from 1966 to 1974.** (Pol) Koszarowski, T. (Instytut Onkologii, ul. Wawelska 15, 02-034 Warsaw, Poland); Gadomska, H. *Przegl Lek* 34(10): 753-758; 1977.

The incidence of malignant breast tumors in Warsaw and in neighboring towns between 1966 and 1974 was investigated. For Warsaw, the av morbidity during this period was 46/100,000, and the incidence was highest in women aged 45-64. Of the total 934 breast cancer patients, 88.8% had infiltrating carcinoma. Surgery and/or radiotherapy were used in most women <79 yr old; above that age, most received symptomatic or no treatment. The 5-yr survival was 125/266 women <45 yr old; 158/374 aged 50-64; 92/295 aged >65. For the surrounding towns, the av morbidity during the period was 19/100,000, and the highest incidence was in women aged 40-69 yr. The predominant histological tumor type in the total 156 patients was infiltrating carcinoma (93.3%), followed by sarcoma (6.0%). Surgery and/or radiotherapy were used in most women <65 yr. Above that age, symptomatic or no treatment predominated. The 5-yr survival was 21/56 women <49 yr old; 21/63 aged 50-64; and 9/37 aged >65 yr. (10 refs.)

**78-1769 Occupational Exposure to Chloromethyl Ethers: A Retrospective Cohort Mortality Study (1949-1972).** (Eng) Pasternack, B. S. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY 10016); Shore, R. E.; Albert, R. E. *Occup Med* 19(11): 741-746; 1977.

The carcinogenicity of the chloromethyl ethers (CME) chloromethyl-methyl ether and bis-chloromethyl ether was evaluated in an epidemiologic study of 1,827 CME-exposed workers at six plants and 8,870 controls. The duration and relative intensity of exposure were classified by job descriptions in company records, which permitted relative magnitude of exposure scores to be assigned for each job category at several plants. Death certificates were obtained for almost all known deaths; and hospital records were obtained, where possible, for cancer-related deaths. There were no differences in non-cancer death rates. An excess of deaths from respiratory cancer was found at one plant, where CME exposures were high. A clear dose-response relationship with risk ratios



ceeding 10 for the longest duration and greatest exposure subgroups was demonstrated for this plant. (25 refs.)

**78-1770 The Treatment of Hyperthyroidism with Iodine-131.** (Eng) Beierwaltes, W. H. (Dept. Internal Medicine, Div. Nuclear Medicine, Univ. Michigan Medical Center, Ann Arbor, MI). *Semin Nucl Med* 8(1): 95-103; 1978.

A follow-up study of 22,000 thyrotoxicosis patients treated with  $^{131}\text{I}$  and 14,000 patients treated surgically or with anti-thyroid drugs showed that the radioisotope did not increase the incidence of leukemia. Moreover,  $^{131}\text{I}$  appeared to decrease the incidence of carcinoma by preventing thyroid cell replication. There is also no evidence that radioiodine therapy of childhood hyperthyroidism or thyroid cancer increases the incidence of infertility or abnormal birth histories. Because of the increased morbidity and mortality from thyroid surgery in children,  $^{131}\text{I}$  is the preferred treatment for thyrotoxicosis in children and adolescents. The persistence of goiter after 'cure' usually signals the presence of coexisting Hashimoto's struma. (42 refs)

**78-1771 Bovine Leukemia and Public Health (Meeting Abstract).** (Eng) Lloyd, J. O. (Beltsville, MD). *J Am Vet Med Assoc* 171(10): 1099; 1977. (no refs.)

**78-1772 Epidemiological Analysis of the Association Between Leukemia and Lymphoma Incidence and X-Ray Diagnostic Loads.** (Rus) Osechinsky, I. V. (Lab. Epidemiology and Histopathology Leukemias, Central Inst. Hematology and Blood Transfusion, Moscow, USSR); Shkanakina, T. P. *Probl Gematol Perelivan Krovi* 23(1): 13-17; 1978.

In an attempt to estimate the effect of x-ray diagnostic loads on the incidence of lymphomas and leukemias, a long-term epidemiologic study was carried out in Kirov Oblast (USSR). Between 1961 and 1972, a total number of about nine million diagnostic x-ray examinations (DRE) was performed; on av each individual underwent 6.9 DRE and received av bone marrow dose (ABMD) of 1.5 rads (dose range from 0.5 to 4.2 rads) and av gonadal dose of 0.2 rads (dose range from 0.1 to 0.6 rads). The association between the DRE and various morbidity indices was measured by correlation coefficient. There was a significant correlation between ABMD

and the incidence of leukemias (0.366) but not with the incidence of lymphomas (0.062). (16 refs.)

**78-1773 Occupational Characteristics of Patients with Leukemia and Lymphogranulomatosis.** (Rus) Plotnikov, Yu. K. (First Dept. Hosp. Therapy, D. I. Ulyanov Medical Inst., Kuibyshev, USSR). *Probl Gematol Perelivan Krovi* 23(1): 18-21; 1978.

The results of a retrospective epidemiologic study of leukemia and lymphogranulomatosis (LG) in Kuibyshev Province, USSR, are presented. Between 1965 and 1974, leukemia or LG was diagnosed in 1,165 patients: there were 314 patients with acute leukemia, 220 with chronic myeloid leukemia, 388 with chronic lymphoid leukemia, and 239 with LG. The patients answered a special questionnaire concerning occupation, length of employment, exposure to various health hazards, etc. The number of petroleum industry employees and employees who had an occupational exposure to organic solvents and dyes was 1.3 times higher in the patients than in the control (healthy) population. Of 140 patients in this occupational group, 31 worked for 3-7 yr, 43 for 8-12 yr, and 66 for > 12 yr. Twenty-three patients had occupational exposure to ionizing radiation or an ultrahigh-frequency (UHF) electromagnetic field: duration of exposure ranged from 3 to 7 yr in 5 patients, 8 to 12 yr in 7, and > 12 yr in 11. These data indicate that prolonged exposure to petroleum products, organic solvents, and UHF and ionizing radiation increases the relative risk for leukemia and LG. (24 refs.)

**78-1774 Incidence of Hemoblastoses in Various Ethnic Groups in Kirghiz SSR Between 1966 and 1974.** (Rus) Mirrakhimov, M. M. (First Dept. Faculty Therapy, Kirgiz Medical Inst., Frunze, USSR); Rakhimova, S. A. *Probl Gematol Perelivan Krovi* 23(1): 9-13; 1978.

The results of an epidemiologic survey of the incidence of various forms of hematoblastosis in Kirgiz SSR, USSR, are presented. Between 1966 and 1974, hematoblastosis was recorded in 2,133 patients ( $9.2/10^5$ ). There were 901 Russians ( $11.7/10^5$ ), 633 Kirgizes, ( $5.5/10^5$ ), 186 Uzbeks ( $6.2/10^5$ ), and 413 persons of other nationalities. The incidence of acute leukemias was relatively higher among the Kirgiz patients than among the Russians (45% and 26%, respectively), but chronic leukemias were more frequent among the Russians (34%, compared to 18% among the Kirgizes). The incidence of chronic lymphoid leukemia was only 2% among the Kirgiz population (compared to 12% among the Russians). These findings indicate that ethnic factors may play a role in the etiology of hemoblastosis. (9 refs.)



**78-1775 Geographical Distribution of the Incidence of Hemoblastosis in the Soviet Union (Analysis of Random Samples).** (Rus) Khokhlova, M. P. (Central Inst. Hematology and Blood Transfusion, Moscow, USSR); Yashanova, N. D.; Osechinsky, I. V.; Martirosov, A. R.; Abdushelishvili, R. G.; Alkhutova, G. I.; Bebesko, V. G.; Bogdanov, I. S.; Bradavichene, M. R.; Voskresenskaya, A. L.; Vygovskaya, Ya. I.; Grinchenko, A. I.; Danilov, I. P.; Dostovalova, L. A.; Zedgenidze, I. Sh.; Logvinenko, A. S.; Mazurok, A. A.; Malviste, R. T.; Mirrhakhimov, M. M.; Morova, L. G.; Muradova, I. V.; Petrosyan, Zh. S.; Plotnikov, Yu. K.; Rakhimova, S. A.; Rozanova, L. M.; Rozova, M. V.; Sedov, K. R.; Sedykina, E. I.; Stepanyan, R. M.; Terebkova, Z. F.; Tuguzbaeva, G. F.; Uzunyan, L. Kh.; Fomina, R. F.; Khakhimov, Kh. A.; Shatrova, M. M.; Shkanakina, T. P. *Probl Gematol Perelivan Krovi* 23(1): 3-9; 1978.

According to a cooperative epidemiological survey of hemoblastosis (HB) in the Soviet Union between 1968 and 1974, 23,065 primary cases of HB were diagnosed. The incidence of HB and its nosologic variants showed geographical variability. A max range of variability was detected for chronic

lymphoid leukemia (0.2-4.3 cases/10<sup>3</sup>), but chronic myeloid leukemia showed more or less a uniform distribution (0.6-1.0 cases). (16 refs.)

*See also:*

- \*(Rev.): 78-1203, 78-1210, 78-1217, 78-1218, 78-1219, 78-1220, 78-1221, 78-1222, 78-1223, 78-1224, 78-1226, 78-1227, 78-1230, 78-1231, 78-1232, 78-1255, 78-1263, 78-1267, 78-1269, 78-1270, 78-1273.
- \*(Chem.): 78-1293, 78-1322, 78-1340, 78-1341, 78-1352, 78-1361, 78-1379, 78-1400, 78-1464, 78-1474, 78-1496, 78-1500, 78-1502, 78-1504, 78-1505, 78-1506, 78-1537.
- \*(Phys.): 78-1527, 78-1529, 78-1531, 78-1532, 78-1537.
- \*(Viral): 78-1626, 78-1645, 78-1648.
- \*(Immun.): 78-1710.
- \*(Path.): 78-1712, 78-1717, 78-1720, 78-1721, 78-1740, 78-1742, 78-1749.



## MISCELLANEOUS

776 **Early Appearance and Mitotic Activity of Multinucleated Giant Cells in Mice after Combined Injection of Talc and Prednisolone Acetate. A Model for Studying Rapid Histiocytic Polykaryon Formation In Vivo.** (Eng) Dreher, R. (Inst. Pathology, Freiburgstrasse 30, Univ. of Bern, 3010 Bern, Switzerland); Keller, H. U.; Hess, M. W.; Moser, B.; Cottier, H. *Lab Invest* 38(2): 149-156; 1978.

Factors involved in the formation and mitotic activity of multinucleated giant cells (MGC) were examined in 4-wk-old C57BL/6 mice treated with talc and a crystalline suspension of prednisolone acetate (PA). Animals were treated with 2 ml of 0.9% saline (controls), talc (20 mg in 2 ml saline, ip), talc + PA, and talc + supernatant of commercial PA. Talc + PA resulted in the formation of significant numbers of MGC within 48 hr. Neither one of these two agents had a comparable effect when injected alone. The MGC arose by cell fusion, and synchronous nuclear division could be observed in a considerable proportion of the newly formed MGC. Although the late prophase was usually normal, high proportions of abnormal mitotic figures were observed at later stages of mitosis, particularly in anaphase and telophase. The chromosome abnormalities were so severe that it is unlikely that mitosis led to successful nuclear multiplication within a given cell. To evaluate whether the enhancing capacity of PA was due to the presence of crystals of a certain size and/or a certain chemical structure, experiments were conducted with crystalline suspensions of several other steroids. Similar to PA, prednisone elicited the formation of MGC when it was injected with talc. However, MGC were not formed with cortisone acetate, cortisone, or testosterone isobutyrate. (1 refs)

777 **Cell Cycle Regulation by Growth Factors and Nutrients in Normal and Transformed Cells.** (Eng) Paul, D. (Fels Research Inst., Temple Univ. Medical School, Philadelphia, PA, 19140); Brown, K. D.; Rupniak, J. T.; Ristow, H. J. *In Vitro* 14(1): 76-84; 1978.

Factors involved in the control of DNA synthesis initiation were studied, and the results for cell lines, primary cultures, and early transfer cultures were compared. Simian virus 40-transformed 3T3 cells (SV3T3), which were originally responsive to epidermal growth factor (EGF) and displayed density-dependent inhibition of growth, lost their responsiveness to EGF after several passages and proliferated without restriction. However, they continued to display EGF receptor sites at the cell surface. Primary Fischer 344 rat hepatocytes were not stimulated by EGF, but the cells bound it to an extent comparable to that of responsive 3T3 cells. Therefore, the presence of EGF receptors does not imply cellular respon-

siveness to the growth factor.  $\text{Ca}^{+2}$  levels appear to be involved in cell proliferation in various primary and secondary Fischer 344 rat hepatocyte cultures. In 3T3-4a cells, however,  $\text{Ca}^{+2}$  levels are not linked to initiation of DNA synthesis; the effects of growth factors are not mediated by extracellular  $\text{Ca}^{+2}$  ions, but they do have a  $\text{Ca}^{+2}$ -sensitive restriction point in  $G_1$ . Studies with primary and secondary cultures indicated that polyamine levels are not tightly coupled to DNA synthesis initiation. Therefore, ornithine decarboxylase induction in  $G_1$ -arrested cells after growth stimulation is not essential for initiation of the growth cycle. Normal, but not transformed, 3T3 cells have a spermidine/spermine-sensitive restriction point in  $G_1$ . Although ribosomal RNA levels appear to be necessary for the induction of proliferation, accumulation of RNA is not essential for the initiation of DNA synthesis. (59 refs)

78-1778 **A Mathematical Model of Periodic Processes in Membranes (With Application to Cell Cycle Regulation).** (Eng) Chernavskii, D. S. (P.N. Lebedev Physical Inst., Acad. Sciences, Moscow, USSR); Palamarchuk, E. K.; Polezhaev, A. A.; Solyanik, G. I.; Burlakova, E. B. *Biosystems* 9(4): 187-193; 1977.

A mathematical model for regulating the cell cycle by the plasma membrane, based on the hypothesis that structural transitions in the cell membrane play an important role in regulation of cell division, is presented. It is suggested that the hard skeleton existing in the membrane of normal cells is absent in the membrane of tumor cells; this conclusion is in accordance with experimental data. (21 refs)

78-1779 **A Cell Aggregation Method for the Selection of Transformed Cells (Meeting Abstract).** (Eng) Steuer, A. F. (Biotech Res. Lab., Rockville, MD, 20852); Hentosh, P. M.; Pan, P. S.; Ting, R. C. *Proc Am Assoc Cancer Res* 19: 106; 1978. (1 ref)

78-1780 **Molecular Changes in Lipoproteins Isolated from Cell Surface Membranes of Morris Hepatoma 16 (Meeting Abstract).** (Eng) Dnistrian, A. M. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Barclay, M.; Terebus-Kekish, O.; Archibald, F. M.; Morris, H. P. *Proc Am Assoc Cancer Res* 19: 156; 1978. (no refs)



- 78-1781 Characterization of the Cell Coat of Ehrlich Ascites Tumor Cells.** (Eng) Rittenhouse, H. G. (Dept. Biological Chemistry, Univ. Michigan, Ann Arbor, MI, 48109); Rittenhouse, J. W.; Takemoto, L. *Biochemistry* 17(5): 829-837; 1978.

The spontaneous release of cell surface material from Ehrlich ascites tumor cells was studied by investigating the release rate of surface-iodinated proteins from lactoperoxidase-labeled cells into isotonic buffer. More than 50% of the cell-associated radioactivity was released from the cells after 60 min at 4 C. These experimental conditions allowed for max removal of surface proteins with minimal cell damage, and they were employed to obtain a subcellular fraction that was operationally defined as the cell coat (glycocalyx). The glycocalyx fraction was characterized by the presence of a highly active aminopeptidase (leucyl  $\beta$ -naphthylamidase) and large amounts of glycoproteins and glycosaminoglycans. In contrast to the purified plasma membranes, the glycocalyx fraction contained essentially no (Na<sup>+</sup>, K<sup>+</sup>)-ATPase activity and little or no sialic acid and cholesterol. 5'-Nucleotidase and alkaline phosphatase were present in low activity in Ehrlich cells and were distributed in both plasma membrane and glycocalyx fractions, although to a lesser extent in the latter. Electrophoresis and staining of the glycocalyx fraction revealed the presence of only one heavily stained band (mol wt 130,000) and multiple lightly stained bands, but the plasma membranes contained numerous heavily stained bands with approx mol wts of 60,000-130,000 and 300,000. Thus, under appropriate conditions, Ehrlich ascites tumor cells rapidly and spontaneously shed a large portion of their cell surface while retaining cell viability. The glycocalyx layer can be routinely fractionated from cells and treated as a biochemically distinct entity from the surface membrane. (60 refs)

- 78-1782 An Effect of ATP on the Permeability of Transport-competent Plasma Membrane Vesicles from Mouse Fibroblasts.** (Eng) Lever, J. E. (Salk Inst., P.O. Box 1809, San Diego, CA, 92112). *Biochem Biophys Res Commun* 79(4): 1051-1058; 1977.

The effect of ATP on the transport activity of plasma membrane vesicles isolated from nontransformed BALB/c mouse embryo fibroblasts and a clonal line of simian virus 40-transformed BALB/c 3T3 cells was investigated. The ability of vesicles to catalyze alanine accumulation across a membrane in the presence of an NaCl gradient was abolished when the vesicles were incubated with 5 mM ATP and 5 mM MgCl<sub>2</sub>. A similar effect was also produced by deoxy-ATP and ADP; however, inhibition was not produced when the  $\alpha$ - $\beta$ - or  $\beta$ - $\gamma$ -methylene ATP derivatives were substituted for ATP. Both nontransformed and virus-transformed fibroblast membrane vesicles showed susceptibility to alanine transport inhibition. Purified plasma membrane vesicles also had a lesser sensitivity to ATP inhibition than less purified preparations. This inhibitory effect was also observed for the transport of other small molecules, including phosphate ion and

uridine. ATP did not disrupt the integrity of the membrane during inhibition. The purified membrane vesicles contained an endogenous protein kinase activity that catalyzed autophosphorylation of membrane proteins in the presence of ATP. Membrane phosphorylation but not transport activation showed slight stimulation by cyclic AMP at pH 6.5, but not at pH 7.5. These results suggest that an intracellular compartment proximal to the plasma membrane may be directly involved in modulating membrane transport independently of its role in controlling (Na<sup>+</sup> + K<sup>+</sup>) ATPase activity. (18 refs)

- 78-1783 Surface ATPase Activity at Cell-Cell Contacts in Hepatic Parenchymal Cells and in Cultured Hepatoma Cells in Monolayer Culture.** (In Japanese) Yamaguchi, K. (Biological Lab., Dept. Life Chemistry, Tokyo Inst. Technology, Meguro, Tokyo, Japan); Ohnishi, T. *Histochemistry* 54(3): 191-199; 1977.

The surface activity of Mg<sup>2+</sup>-ATPase at the cell-cell contacts of hepatic parenchymal cells in monolayer culture was determined. The effect of dibutyl cyclic AMP (dbcAMP) and theophylline on cell growth was examined in Yoshida ascites hepatoma 66 cells maintained in Donryu rats. In the presence of 1 mM theophylline and 1 mM dbcAMP, the hepatoma cells reached saturation density at 2 x 10<sup>5</sup> cells/cm<sup>2</sup>. Once saturation density was reached, removal of theophylline and dbcAMP led to a rapid release from controlled growth. The orientation of the cells was not affected by treatment, but treated cells were noticeably larger than the untreated cells. dbcAMP/theophylline-treated cells lacked localization of intense ATPase activity at cell-cell contacts; however, removal of the additives resulted in recovery of intense ATPase activity. It is suggested that the increase in ATPase activity in prime hepatoma cells for release from contact inhibition is growth. No enzyme activity was noted without Mg or ATP and with  $\beta$ -glycerophosphate as a substrate. Yoshida ascites hepatoma 7974 cells, which are less malignant than hepatoma 66 cells and which form cellular islands (small tissue masses of > 10 cells), had weak ATPase activity on the surface of cell-cell contacts. A rise in activity was not observed with time. Cells that detach and form new islands have high ATPase activity. ATPase activity at the surface of cell-cell contacts of normal hepatic parenchymal cells was low at confluency. (18 refs.)

- 78-1784 The Role of Adenosine 3',5'-Cyclic Monophosphate in the Density-dependent Regulation of Growth and Tyrosinase Activity of B-16 Melanoma Cells.** (Eng) Wade, D. R. (Dept. Physiology, Southern Illinois Univ. Sch. Medicine, Carbondale, IL, 62901); Burkart, E. *J Cell Physiol* 94(3): 265-274; 1978.

The role of cyclic AMP (cAMP) in the density-dependent regulation of growth and tyrosinase (TS) activity was investigated in B-16 F<sub>11</sub> and B-16 melanoma cells. The latter



population doubling time twice that of the former. Incubation of the cells with 0.1 mM 1-methyl-3-isobutylxanthine (IX) produced a sustained rise in intracellular cAMP that preceded an increase in the specific (TS) activity. Cultures of the two clones showed density-dependent growth inhibition. The TS activity of each line increased progressively during logarithmic growth, reaching peak values shortly after confluence. The stimulatory effects of MIX and confluence on TS were additive. Intracellular cAMP levels fell during logarithmic growth, and they were minimal in confluent cultures. Cells plated at high density had lower TS activity than cells allowed to achieve a similar density by successive division of sparsely planted cultures; however, the intracellular cAMP levels of these cultures were not different. These findings suggest that agents that increase intracellular cAMP concentrations can inhibit cell division and stimulate TS activity. Thus, the elevation of TS activity at confluence is not mediated by cAMP. (37 refs)

**78-1785 Vitamin A Serum Levels and Dietary Vitamin A Intake in Lung Cancer Patients.** (Eng) Cohen, H. (NCI-VA Medical Oncology Branch, Veterans Affairs Hosp., Washington, DC, 20422); Primack, A.; Broder, E.; Williams, L. R. *Cancer Lett* 4(1): 51-54; 1978.

Serum vitamin A levels were determined in 67 patients (64 men, 3 women) with newly diagnosed, histologically proved, resectable lung cancer. Although vitamin A intake varied considerably from patient to patient, 66 patients had serum vitamin A levels within the normal range. There were no differences in levels between patients with regional or disseminated disease, and there were no differences in levels in patients with and without metastatic disease to the liver. These findings suggest that a vitamin A deficiency is not implicated in pulmonary carcinogenesis. (12 refs)

**78-1786 Retinoic Acid-induced Changes in Saturation Density and Adhesion of Transformed Mouse Fibroblasts (Meeting Abstract).** (Eng) Adamo, S. (NIH, Bethesda, MD, 20014); Akalovsky, I.; De Luca, L. M. *Proc Am Soc Cancer Res* 19: 27; 1978. (no refs)

**78-1787 Calcium Stimulation of Plasminogen Activator Secretion/Production by Swiss 3T3 Cells.** (Eng) Gou, I. N. (Infectious Disease Unit, Massachusetts General Hosp., Boston, MA 02114); Roblin, R. O.; Black, P. H. *J Biol Chem* 252(18): 6256-6259; 1977.

Actively growing Swiss 3T3 cells secrete high levels of plasminogen activator (PA) that decrease after the cells become confluent. In contrast, simian virus 40-transformed 3T3 cells (SV3T3 cells) secrete large amounts of PA independent of cell

density. To determine if active cell multiplication correlates with PA secretion, 3T3 and SV3T3 cells were incubated in serum-free medium containing different concentrations of  $\text{Ca}^{2+}$ . Treatment of both subconfluent and confluent 3T3 cells with high  $\text{Ca}^{2+}$  concentrations (3.0-4.9 mM) increased the amount of both secreted and cell-associated PA in a dose-dependent manner. In addition, the ionophore A23187 (19-95 nanomolar), in the presence of a normal  $\text{Ca}^{2+}$  level (1.8 mM) stimulated both the production and secretion of PA from growing 3T3 cells. The  $\text{Ca}^{2+}$  stimulation of PA production/secretion may be related to the mitogenic effect of  $\text{Ca}^{2+}$ . The SV3T3 cells did not respond to  $\text{Ca}^{2+}$  stimulation of PA secretion, suggesting that neoplastic transformation may involve an alteration of the calcium regulatory function. (30 refs.)

**78-1788 Modulation of Motility in Malignant and Non-malignant Cells by Trypsin Inhibitors and Inhibition of Plasminogen Activation (Meeting Abstract).** (Eng) Varani, J. (Dept. Pathology, Univ. Connecticut Health Center, Farmington, CT); Orr, W.; Ward, P. A. *Fed Proc* 37(3): 486; 1978. (no refs)

**78-1789 Surface Glycosaminoglycans and Calcium Distribution in 3T3 Cells.** (Eng) Vannucchi, S. (Istituto di Patologia Generale e di Microbiologia, Università degli Studi, Viale Morgagni, Firenze, Italy); Del Rosso, M.; Cella, C.; Urbano, P.; Chiarugi, V. *Biochem J* 170(1): 185-187; 1978.

The 3T3 cell line was studied to determine whether changes in the composition of the cell-coat glycosaminoglycans, which take place during growth and transformation, are paralleled by changes in the distribution of cellular calcium ( $\text{Ca}^{2+}$ ). Resting 3T3 cells had relatively more sulfated glycosaminoglycans and  $\text{Ca}^{2+}$  in their cell coat than did growing or simian virus 40 (SV40)-transformed cells. The intracellular concentration of  $\text{Ca}^{2+}$  in resting 3T3 cells might be lower than that in growing or SV40-transformed cells, as suggested by the high  $\text{Ca}^{2+}$  influx on treatment with trypsin. The variations in the glycosaminoglycan composition of the cell coat may affect the content and distribution of  $\text{Ca}^{2+}$  in and around any given cell, by virtue of the different avidities of the cell-coat components for this ion. The evidence supports the ideal that the role of  $\text{Ca}^{2+}$  in the control of cellular activities is regulated by its cellular distribution and that its intra- and extracellular concentrations may be inversely related. (12 refs)

**78-1790 Changes in the Hybridization of Rapidly Labeled Ribonucleic Acids During Tumor Progression.** (Rus) Shaposhnikov, I. A. D. (Lab. Biochemistry, Inst. Oncology USSR Ministry Public Health, Leningrad, USSR); Ratovitskii, E. A. *Tsitologiya* 19(8): 888-893; 1977.



The hybridization of in vivo-labeled nuclear and mitochondrial RNA's from a diethylnitrosamine-induced hepatoma (MD) of C3HA mice with nuclear DNA from the liver of tumor-free C3HA mice was studied during sc isologous passages. The RNA's were labeled by ip injection of  $^{14}\text{C}$ -orotic acid into the mice 40 min before they were sacrificed. During the early (5th and 6th) passages, the labeled nuclear RNA's contained only a few nucleotide sequences that were hybridizable with nuclear DNA's from normal mice. The amount of the hybridizable nucleotide sequences increased with tumor progression (60th passage); ie, the initial repression of the nuclear genome was followed later by a derepression. The hybridizability of the mitochondrial RNA's with nuclear DNA's remained practically the same over the subsequent passages. (18 refs)

**78-1791 Sequence Diversity of Total Poly(A)-Containing RNA from Mouse Simple Embryoid Bodies and Teratocarcinomas (Meeting Abstract).** (Eng) Harris, S. E. (Lab. Environmental Toxicology, NIEHS, Research Triangle Park, NC, 27709; Gipson, S.; Tully, D.; Silverberg, A. B. *Environ Health Perspect* 20: 237-238; 1977. (no refs)

**78-1792 Heterologous In Vitro Protein Synthesis for Detection of Specific mRNAs (Meeting Abstract).** (Eng) Silverberg, A. B. (Lab. Environmental Toxicology, NIEHS, Research Triangle Park, NC, 27709); Harris, S. E. *Environ Health Perspect* 20: 238; 1977. (no refs)

**78-1793 Increased Abundance of Specific mRNA and Cytosol Proteins in Rapidly Growing Tumors (Meeting Abstract).** (Eng) Busch, H. (Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030); Hirsch, F. W.; Morris, H. P.; Nall, K. N.; Raju, K. S.; Johnson, S. A.; Spohn, W. H.; Takami, H. *Proc Am Assoc Cancer Res* 19: 100; 1978. (2 refs)

**78-1794 Post-Transcriptional Modification Sites in 18S rRNA in Novikoff Hepatoma Cells (Meeting Abstract).** (Eng) Choi, Y. C. (Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030); Busch, H. *Proc Am Assoc Cancer Res* 19: 189; 1978. (no refs)

**78-1795 Detection in Human Ovary and Prostate Tumors of DNA Polymerase Activity that Copies Poly(2'-O-methylcytidylate)-oligodeoxyguanylate.** (Eng) Gerard, G. F. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, 3681 Park Ave., St. Louis, MO, 63110); Loewenstein, P. M.; Green, M. *Cancer Res* 38(4): 1008-1011; 1978.

Samples of 16 malignant and 9 nonmalignant human ovaries and 16 malignant and 1 nonmalignant prostate glands were assayed for DNA polymerase activity using a synthetic template primer specific for viral reverse transcriptase, poly(2'-O-methylcytidylate)-oligodeoxyguanylate. Particulate DNA polymerase activity copying this primer and banding at a density of 1.1 to 1.20 g/ml in sucrose gradients was detected in 8/16 malignant ovary samples and 11/16 malignant prostate samples. None of the nonmalignant samples showed significant amounts of this polymerase. None of the ovarian samples contained terminal transferase activity, but two of the prostate carcinomas were positive for this enzyme. The significance of this finding is not known. It is concluded that a significant proportion of human ovary and prostate malignant tumors contain particle-associated reverse transcriptase (25 refs)

**78-1796 DNA Polymerases in Liver and Hepatoma Nuclei (Meeting Abstract).** (Eng) Coetzee, M. L. (Dept. Anatomy and Cell Biology, Univ. Pittsburgh, Pittsburgh, PA, 15261); Ove, P. *Proc Am Assoc Cancer Res* 19: 3; 1978. (no refs)

**78-1797 Nuclear DNA Polymerases in Colonic Epithelial Cells of Rat During Induction of Large Bowel Cancer (Meeting Abstract).** (Eng) Chiu, J. F. (Dept. Biochemistry, Vanderbilt Univ., Nashville, TN, 37232); Jones, J.; Markert, C.; Decha-Umphai, W. *Proc Am Assoc Cancer Res* 19: 169; 1978. (1 ref)

**78-1798 DNA Content, Cell Size, and Malignancy (Meeting Abstract).** (Eng) Suzuki, N. (M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Withers, H. R.; Williams, M. *Proc Am Assoc Cancer Res* 19: 186; 1978. (2 refs)

**78-1799 Fidelity of DNA Synthesis In Vitro: Effects of Depurination (Meeting Abstract).** (Eng) Shearman, C. W. (Inst. Cancer Res., Fox Chase Cancer Center Philadelphia, PA, 19111); Loeb, L. A. *Proc Am Assoc Cancer Res* 19: 7; 1978. (no refs)

**78-1800 DNA and RNA Synthesis in Zinc-Deficient Ehrlich Cells (Meeting Abstract).** (Eng) Saryan, L. A. (Dept. Chemistry, Univ. Wisconsin-Milwaukee, Milwaukee, WI, 53201); Petering, D. H. *Proc Am Assoc Cancer Res* 19: 163; 1978. (no refs)



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## **EDITOR**

**GEORGE P. STUDZINSKI, M.D., Ph.D.**  
COLLEGE OF MEDICINE AND DENTISTRY  
OF NEW JERSEY, NEWARK

## **ASSOCIATE EDITOR**

**JUSSI J. SAUKKONEN, M.D.**  
JEFFERSON MEDICAL COLLEGE  
PHILADELPHIA

## **NCI STAFF CONSULTANTS**

**ELIZABETH WEISBURGER, Ph.D.**  
**JOAN W. CHASE, M.S.**

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**BRUCE H. KLEINSTEIN, Ph.D., J.D., Assistant Director, Biomedical Projects**

**RUTHANN E. AUCHINLECK, Managing Editor**

**The Franklin Research Center**  
**The Benjamin Franklin Parkway, Philadelphia, Pennsylvania 19103**

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## ABBREVIATIONS

**JOURNAL** names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

**LANGUAGE** of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

**ABBREVIATIONS** used in abstracts:

<b>A</b>	angstrom(s)	<b>mOsm</b>	milliosmolar
<b>ACTH</b>	adrenocorticotrophic hormone	<b>max</b>	maximum
<b>ADP</b>	adenosine diphosphate	<b>mEq</b>	milliequivalent(s)
<b>AMP</b>	adenosine monophosphate	<b>min</b>	minute(s)
<b>ATP</b>	adenosine triphosphate	<b>ml</b>	milliliter(s)
<b>approx</b>	approximately	<b>μl</b>	microliter(s)
<b>av</b>	average	<b>mm</b>	millimeter(s)
<b>BCG</b>	bacillus Calmette-Guerin	<b>mo</b>	month(s)
<b>bid</b>	twice daily	<b>mol wt</b>	molecular weight
<b>C</b>	degree(s) centigrade	<b>N</b>	normal concentration
<b>cal</b>	calorie(s)	<b>NAD</b>	nicotinamide adenine dinucleotide
<b>kcal</b>	kilocalorie(s)	<b>NADH</b>	reduced nicotinamide adenine dinucleotide
<b>cc</b>	cubic centimeter(s)	<b>NADP</b>	nicotinamide adenine dinucleotidephosphate
<b>Ci</b>	curie(s)	<b>NADPH</b>	reduced nicotinamide adenine dinucleotidephosphate
<b>mCi</b>	millicurie(s)	<b>NCI</b>	National Cancer Institute
<b>μCi</b>	microcurie(s)	<b>NIH</b>	National Institutes of Health
<b>cm</b>	centimeter(s)	<b>PAS</b>	periodic acid-Schiff
<b>CNS</b>	central nervous system	<b>po</b>	orally
<b>cpm</b>	counts per minute	<b>ppb</b>	parts per billion
<b>DNA</b>	deoxyribonucleic acid	<b>ppm</b>	parts per million
<b>ED<sub>50</sub></b>	median effective dose	<b>qid</b>	four times daily
<b>EDTA</b>	ethylenediamine tetraacetic acid	<b>qod</b>	every other day
<b>g</b>	gram(s)	<b>QO<sub>2</sub></b>	oxygen quotient
<b>kg</b>	kilogram(s)	<b>R</b>	roentgen
<b>mg</b>	milligram(s)	<b>RBC</b>	red blood cells (erythrocytes)
<b>μg</b>	microgram(s)	<b>RNA</b>	ribonucleic acid
<b>Hb</b>	hemoglobin	<b>rpm</b>	revolutions per minute
<b>hr</b>	hour(s)	<b>sc</b>	subcutaneous
<b>ia</b>	intra-arterial	<b>sec</b>	second(s)
<b>id</b>	intra-dermal	<b>SGOT</b>	serum glutamic-oxaloacetic transaminase
<b>IgA</b>	Immunoglobulin A	<b>SGPT</b>	serum glutamic-pyruvic transaminase
<b>IgB</b>	Immunoglobulin B	<b>soln</b>	solution
<b>IgG</b>	Immunoglobulin G	<b>TCD</b>	tissue culture dose
<b>IgM</b>	Immunoglobulin M	<b>TCD<sub>50</sub></b>	median tissue culture dose
<b>ILS</b>	increased life span	<b>tid</b>	three times daily
<b>im</b>	intramuscular	<b>UV</b>	ultraviolet
<b>ip</b>	intra-peritoneal	<b>WBC</b>	white blood cells (leukocytes)
<b>IU</b>	International Unit(s)	<b>wk</b>	week(s)
<b>iv</b>	intravenous	<b>wt</b>	weight
<b>Km</b>	Michaelis constant	<b>X</b>	times
<b>LD</b>	lethal dose	<b>yr</b>	year(s)
<b>LD<sub>50</sub></b>	median lethal dose		
<b>M</b>	molar		
<b>μM</b>	micromolar		

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## REVIEW

- 1801 **Mechanisms of Carcinogenesis. Dose Response.** (Eng) Gehring, P. J. (Health and Environmental Sciences, Toxicology Res. Lab., Dow Chemical USA, Midland, TX); Blau, G. E. *Cancer Bull* 29(6): 152-161; 1977.

A model for predicting the carcinogenic effect of low doses of chemicals to humans is presented. This model can be used as a basis for other models that allow for absorptive and distributive processes or exclude the activation step if a chemical does not require activation. The major problem with the model is that it employs only one mechanism, alkylation of genetic material, for carcinogenesis. (27 refs)

- 1802 **Current Concepts on Mechanisms of Chemical Carcinogenesis.** (Eng) Weinstein, I. B. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY). *Cancer Bull* 29(6): 144-152; 1978.

A review of current concepts on the mechanisms of chemical carcinogenesis reveals that there is a great diversity in the structures of the chemicals that cause cancer in humans. These include not only industrial chemicals, but also chemical mixtures, drugs, and naturally occurring compounds. In order to exert their carcinogenic effect, many of these require conversion to a highly reactive electrophilic species that can then react with proteins and nucleic acids to form covalent adducts. The multistep nature of this process and the role of promoting agents, hormones, nutritional factors, and other factors in carcinogenesis are examined. In vitro systems may reveal the key to carcinogenesis and the roles of diverse agents at the various steps in this process. (42 refs)

- 1803 **Mechanisms of Tumor Induction in Light of the General Theory of Oncogenesis.** (Rus) Meckler, B. (Moscow, USSR). *Usp Sovrem Biol* 85(1): 134-151; 1978.

Various aspects of chemical, radiation, viral, and hormonal carcinogenesis; implantation tumorigenesis; and tumor development in autoimmune diseases, precancerous states, and aging are discussed in light of the general theory of oncogenesis (the rationale of the theory is described elsewhere). It is postulated that interaction of chemical carcinogens with the membrane proteins rather than with the DNA molecule results in cellular transformation. In viral carcinogenesis, insertion of a protein coded for by the viral nucleic acid into the cellular membranes, and not

incorporation of the viral and cell genomes per se, is responsible for malignant or benign transformation. The latter occurs if the viral genome lacks the gene identical to the host genes, which code for the tissue- or organ-specific membrane proteins. (92 refs)

- 78-1804 **Chemical Carcinogenesis in Syrian Hamsters.** (Eng) Homburger, F. (Bio-Res. Inst., Cambridge, MA, 02141); Adams, R. A.; Soto, E.; Van Dongen, C. G. *Fed Proc* 37(7): 2090-2092; 1978.

The susceptibility of various inbred strains of Syrian hamsters to chemical carcinogenesis is reviewed. Inbred BIO hamsters show marked strain differences in susceptibility to polycyclic hydrocarbons injected sc, ingested into the gastrointestinal tract, and reaching the mammary gland. There are also strain differences in susceptibility to gastric carcinogenesis by methylcholanthrene (MC), to urinary bladder carcinogenesis by  $\beta$ -naphthylamine, and to laryngeal carcinogenesis following cigarette smoke inhalation. No correlation has been observed in these strains between hepatic aryl hydrocarbon hydroxylase activity and carcinogen susceptibility. Sex differences also exist: 60% of BIO 15.16 males but none of the females, develop intestinal cancers with MC gavage. Animals with a high susceptibility to MC by gavage generally show a high susceptibility to sc administered polycyclic hydrocarbons. The line most susceptible to polycyclic hydrocarbons, BIO 15.16, was the line most resistant to  $\beta$ -naphthylamine-induced bladder cancer. These strain and sex differences in susceptibility to chemical carcinogens, combined with a low incidence of spontaneous tumors, make hamsters an excellent model for the study of susceptibility and resistance to carcinogens. (19 refs)

- 78-1805 **Comparison of Spontaneous Soft Tissue Hamster Tumors with Those Induced by Viral and Chemical Carcinogens.** (Eng) Berman, L. D. (Lab. Service, Boston Veterans Admin. Hosp., Mallory Inst. Pathology, Boston, MA, 02130); Soto, E. *Fed Proc* 37(7): 2089-2090; 1978.

Spontaneous, virus-induced, and chemical-induced tumors in hamsters were compared based on a review of the literature. Adenoviruses produce characteristic small cell tumors that tend to form palisades of cells around capillaries and small islands of stroma. They have been classified as neurogenic in origin. Soft tissue tumors induced by polyoma virus vary



from undifferentiated spindle cell sarcomas to tumors showing easily discernible differentiation toward mature mesenchymal elements. Simian virus 40 (SV40) and BK virus induce tumors varying in composition from undifferentiated spindle cell sarcomas to fibrosarcomas. Bovine papilloma virus induces fibromas or low-grade fibrosarcomas of the dermis. The Rous sarcoma and murine sarcoma viruses produce undifferentiated spindle cell and round cell sarcomas that have been classified as rhabdomyosarcomas and of histiocytic origin, respectively. Polycyclic hydrocarbons induce large cell spindle cell sarcomas resembling those induced by SV40. N-Methyl-N-nitrosourea induces undifferentiated tumors composed of small spindle cells and larger round cells, and thorium dioxide induces undifferentiated spindle cell sarcomas that are similar to the polycyclic hydrocarbon tumors. A total of 71% of the spontaneous tumors are moderately to well-differentiated sarcomas of varying types with no unusual features. Other types of spontaneous tumors include leiomyosarcomas, rhabdomyosarcomas, angiosarcomas, hemangiopericytomas, and liposarcomas. It is unlikely that any spontaneous soft tissue tumors could have been induced by a known oncogenic agent. (13 refs)

- 78-1806 Clinical Assessment of Laboratory Rodents on Long Term Bioassay Studies.** (Eng.) Fox, J. G. (Div. Lab. Animal Medicine, Massachusetts Inst. Technology, Cambridge, MA, 02139). *J Environ Pathol Toxicol* 1(2): 199-226; 1977.

The disease status of laboratory rodents should be assessed clinically before the animals are placed on toxicological bioassay programs, particularly when the stress of dietary or parenteral intake of toxic substances may trigger the clinical onset of latent diseases in research animals. Environmental influences on the biochemical, physiological, and behavioral status of the animals must be monitored continually. Temperature, humidity, ventilation, lighting, and the microenvironment of the cage will all affect the response of the animal to various microbial or chemical insults. Unwanted variables in the diet can also alter the biological response of the animal. Adequately trained personnel must be available to provide daily care, clinical observation, and necessary treatment if signs of illness are noted. Clinical signs of common diseases in the integument, sensory organs, and mammary glands, and the digestive, respiratory, urogenital, hematopoietic, and nervous systems are described. The significance of the disease is assessed in relation to the overall health of the animal and the interpretation of experimental results. (128 refs)

- 78-1807 Principles Underlying Testing for Carcinogenicity.** (Eng) Clayson, D. B. (Eppley Cancer Inst., Univ. Nebraska Medical Center, Omaha, NB). *Cancer Bull* 29(6): 161-166; 1977.

In vitro tests are important methods of evaluating the carcinogenicity of a given chemical in view of the high cost, period of time, and species specificity of similar experiments with animals. It is suggested that a battery of short-term involving both microbial and mammalian cell mutagenesis, cell transformation, and DNA repair can be used to screen potential carcinogens. (18 refs)

- 78-1808 Evaluation of the Carcinogenicity of Chemicals: A Review of the Monograph Program of the International Agency for Research on Cancer (1971 to 1977).** (Eng) Tomatis, L. (International Agency Res. Cancer, Cours Albert Thomas, 69372 Lyon Cedex 2, France); Auer, C.; Bartsch, H.; Huff, J.; Montesano, R.; Saracci, R.; Watanabe, E.; Wilbourn, J. *Cancer Res* 38(4): 877-885; 1978.

The International Agency for Research on Cancer has reviewed 368 chemicals for carcinogenicity, and 26 have been found to be carcinogenic in man. A total of 221 were carcinogenic in at least one animal species, but there were either no epidemiological studies available for man or the human evidence was inconclusive. For the remaining 121, the available data were inadequate for evaluation of a carcinogenic effect in animals or humans. (50 refs)

- 78-1809 Iron, Zinc, Free Radicals and Oxygen in Tumor Disorders and Cancer Control.** (Eng) Wills, R. L. (Biochemistry Dept., Brunel Univ., Uxbridge, Middlesex, England). *Ciba Found Symp* 51: 331-354; 1977.

Evidence that cancer results from the decompartmentalization of iron in the cell prior to or during cell division is presented. Zinc plays a major role in protecting the cell from the damaging effects of decompartmentalized iron. It is suggested that normal cells do not divide until the zinc concentration at critical sites within the cell is sufficient to protect the cells from any decompartmentalized iron that may be present. If the concentration of decompartmentalized iron at critical sites is within normal limits, the increased zinc concentration will protect the cell from iron-catalyzed, free radical-induced damage and normal healthy progeny will be produced. If there is too much free iron, free-radical chain reactions may ensue. If the reactions are extensive, the cell or its progeny will die. However, if an antioxidant is present, particularly if the oxygen concentration is low, the extent of oxidation may be limited and the cell may survive. The genetic apparatus of the cell may have been altered, however, in such a way that the genes that control the ability of the plasma membrane to regulate stimulatory zinc concentrations are damaged so that the progeny cannot increase their zinc concentrations after contact. Uncontrolled proliferation will then occur. This theory may provide a unifying mechanism for the action of many carcinogenic agents. (72 refs)



- 78-1810 Membrane Cation Transport and the Control of Proliferation of Mammalian Cells.** (Eng) Kanner, J. G. (Dept. Biology, Univ. Ottawa, Ottawa K1N 6N5, Canada). *Annu Rev Physiol* 40: 19-41; 1978.

Studies of cell proliferation have indicated that the increased activity of the cation pump in stimulated lymphocytes was accompanied or preceded by a correspondingly greater  $K^+$  efflux. Whether or not the increased pump activity in transformed cell lines is accompanied by a similar  $K^+$  efflux is unknown. The role of  $Na^+K^+ATPase$  in normal, mutant, and transformed cells is also reviewed. (144 refs)

- 78-1811 Metals as Regulators of Heme Metabolism.** (Eng) Maines, M. D. (Rockefeller Univ. Hosp., New York, NY, 10021); Kappas, A. *Science* 198(4324): 1215-21; 1977.

Various trace elements are regulators of heme synthesis, degradation, and cellular content of heme proteins. This control is exerted through initial repression of  $\gamma$ -aminolevulinic acid synthetase, the rate-limiting enzyme in heme synthesis, and induction of heme oxygenase, the rate-limiting enzyme in heme degradation. The decreases in the cellular content of cytochromes P-450 and P-448 induced by trace metals are directly reflected in the ability of cells to carry out drug and carcinogen oxidations that depend on these heme proteins. Thus, trace metal intake can have a severe effect on chemicals that are detoxified or metabolically transformed by the P-450 system. (65 refs)

- 78-1812 Pharmacogenetics: A Possible Pragmatic Perspective in Neoplasm Predictability.** (Eng) Atkinson, S. A. (NIH, Bethesda, MD, 20014); Nebert, D. W. *Semin Oncol* 5(1): 89-106; 1978.

The importance of the drug-metabolizing system in the breakdown of environmental carcinogens is reviewed. The microsomal cytochrome P-450-dependent monooxygenases metabolize many hydrophobic substances, but evidence indicates that although these biotransformations facilitate excretion, they may potentiate carcinogenicity and toxicity. The best example of this is the activation of polycyclic aromatic hydrocarbons to compounds capable of modifying DNA and proteins. The genetic regulation of cytochrome P-450 induction by carcinogens and related compounds is also reviewed, and the evidence that an inheritable variation in the drug-metabolizing system in humans may be a risk factor in susceptibility to cancer is discussed. (112 refs)

- 78-1813 Regulation of the Mammalian Cell Cycle In Vitro?** (Eng) Thomas, D. B. (Natl. Inst. Medical

Res., Ridgeway, Mill Hill, London NW7 1AA, England). *Biochem Soc Trans* 5(6): 1801-1808; 1977.

There is no evidence that cultured cells provide a realistic model of homeostasis in vitro and that normal growth characteristics are altered radically in vitro by transformation with chemical carcinogens or oncogenic viruses. Virus-transformed embryo fibroblasts exhibit striking changes in serum requirements and saturation density that have been attributed to loss of normal growth control. However, fibroblast cell lines are autonomous, immortal (rodent and hamster), and lack a viable  $G_0$  state. (87 refs.)

- 78-1814 Genetic and Microbiological Factors in the Control of Carcinogenesis in Animals.** (Rus) Dushkin, V. A. (Scientific Res. Lab. Experimental-Biological Models, Moscow Oblast, USSR); Malashenko, A. M. *Vestn Akad Med Nauk SSSR* (10): 75-76; 1977.

The possible effect of endogenous factors (genotype and microbe content) on carcinogenesis is surveyed briefly. Comparative analysis of the sensitivity of 101/H, C57BL/6, and A/Sn mice to thiophosphamide showed that cytogenetically sensitive C57BL/6 mice had a reduced ability to repair DNA damage. The incidence of spontaneous and induced tumors in germfree mice was 1.5 times less than that in mice with normal intestinal microflora, but the administration of acidophilic bacteria significantly increased the frequency of small intestinal tumors in conventional rats. (no refs)

- 78-1815 Cancer Genetics: A Gordian Knot.** (Eng) Goepfert, C. E. (Dept. Medicine, Jefferson Medical Coll., 1025 Walnut St., Philadelphia, PA, 19107). *Semin Oncol* 5(1): 61-65; 1978.

Once a cell loses the ability to send and/or receive signals like its neighboring cells, it invades local tissue and becomes malignant. The study of cancer genetics is ripe for the uncovering of the mechanisms involved in this transformation. (12 refs)

- 78-1816 Skin, Heredity, and Cancer.** (Eng) Lynch, H. T. (Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, 2500 California St., Omaha, NB, 68178); Frichot, B. C. *Semin Oncol* 5(1): 67-84; 1978.

A general survey of genodermatoses with cancer associations is presented, and concepts emerging in genetics, dermatology, and oncology that may be applied to etiology, carcinogenesis, and cancer control are reviewed. Tables of autosomal dominant and recessive diseases are presented that should assist a physician in the differential diagnosis of patients with der-



matoses. The importance of the clinical application of cutaneous signs, such as cafe au lait spots, is illustrated by a 17-year-old man with neurofibrosarcoma. Special attention is also focused on xeroderma pigmentosum, using a family in which 5/9 siblings were affected by xeroderma pigmentosum (2 of whom were identical twins) and familial malignant melanoma. Recommendations for the diagnosis, management, and control of these diseases are presented. (110 refs)

- 78-1817 Precursor Lesions in Familial Melanoma.** (Eng) Greene, M. H. (Environmental Epidemiology Branch, NCI, Landow 3C-18, Bethesda, MD, 20014); Reimer, R. R.; Clark, W. H.; Mastrangelo, M. J. *Semin Oncol* 5(1): 85-87; 1978.

The importance of precursor lesions in the diagnosis of familial melanoma is discussed. Although familial melanoma generally appears as an autosomal dominant trait, polygenic inheritance has been suggested by a study of several families. Precursor lesions generally number > 100, but some patients may have as few as 10. They generally appear after late adolescence and continue to appear throughout adult life. The nevi are most prominent over the horse collar area of the trunk, are 5-10 mm or larger in diameter, and have an irregular outline. Histologically, areas of atypical melanocytic hyperplasia are interspersed among nests of orderly melanocytes. A study of first-degree relatives of familial melanoma patients indicated that the detection rate of new melanomas among relatives with atypical nevi was 14%. All of these tumors were Clark level 1 or 2 and none recurred following wide excision. (15 refs)

- 78-1818 Multiple Endocrine Neoplasia and the APUD Concept (Letter to Editor).** (Eng) Skrabanek, P. (Endocrine Unit, Mater Misericordiae Hosp., Dublin, Ireland); Powell, D. *Ir Med J* 70(20): 625; 1977.

A review of the literature indicates that of about 40 amine precursor, uptake, and decarboxylase (APUD) cell types, only a few can be shown to originate in the neural crest. The APUD concept cannot be used to explain multiple endocrine neoplasia, as the parathyroid hormone-producing cells do not have APUD characteristics, and they have not been shown to arise in the neural crest. The difficulty in proving the APUD hypothesis is reported. (19 refs)

- 78-1819 The Multiple Endocrine Neoplasia Syndromes: Implications for the Study of Inherited Tumors.** (Eng) Baylin, S. B. (2-127, Oncology Center, Johns Hopkins Hosp., Baltimore, MD, 21205). *Semin Oncol* 5(1): 35-45; 1978.

The origins of the multiple endocrine neoplasia (MEN) syndromes are reviewed. Three such syndromes are recognized: MEN-I, or Wermer's syndrome, is dominated by lesions of the parathyroids, islets of the pancreas, and in the anterior pituitary gland. MEN-II, Sipple's syndrome or MEN-2a, is dominated by medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenomas. MEN-2b, mucosal neuromas syndrome or MEN-2b, is characterized by medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, and intestinal ganglioneuromatosis. It is suggested that the cells involved in these tumors arise from APUD (amine, precursor uptake, and decarboxylase) cells of the neural crest; this evidence is strongest for MEN-II syndrome. Enzymatic studies of a MEN-II patient indicated that his medullary thyroid carcinoma and pheochromocytoma were clonal in origin, suggesting that a mutation in a single cell or very small clone is the final event in the formation of these tumors. It is theorized that a mutational event renders a cell susceptible to infection by an oncogenic virus and that excessive hormone secretions from one MEN lesion cause the other. (64 refs)

- 78-1820 Chromosomal Proteins and the Regulation of Gene Expression in Normal and Neoplastic Cells.** (Eng) Stein, G. S. (Dept. Biochemistry and Molecular Biology, J. Hillis Miller Health Center, Univ. of Florida, Gainesville, FL, 32610); Stein, J. L.; Thomson, J. A. *Mol Cell Res* 1(4): 351-384; 1977.

Genome-associated proteins are characterized and reviewed with respect to their structural and functional properties. Special attention is focused on gene regulation in eukaryotic cells, histones, and nonhistone chromosomal proteins. It has been postulated that cancer is a disease of gene regulation; that, although the causative factors may be varied, the manifestations of the disease are due to the disruption of normal regulatory mechanisms. The major features of cancer cells (invasiveness, metastasis, rapid growth, and escape from the host immune system) are also the characteristics of many embryonic cells; therefore, normal cells contain all the necessary information for the phenotypic expression of malignancy. Furthermore, malignant cells show derepression of genes and express genes that are normally only expressed in other cell types. The mechanisms by which normal control of genetic expression may be heritably altered, changes in nuclear proteins in malignant cells in vivo, and changes in nuclear proteins in transformed cells are discussed. (457 refs)

- 78-1821 Chromosomal Aberrations and the Origin of Tumors.** (Ger) Zankl, H. (Institut für Humangenetik der Universität des Saarlandes, D-6650 Homburg (Saar), W. Germany); Zang, K. D. *Klin Wochenschr* 57(1): 7-16; 1978.



studies of the relationships between chromosome aberrations and the genesis of tumors in humans and animals are reviewed. A sharply increased tumor risk was found in patients with chromosome breakage caused by exogenous or genetic factors and, to a lesser degree, in patients with congenital chromosome aberrations. Increased tumor risk was observed in patients with Down's syndrome and Klinefelter's syndrome. Increased incidence of retinoblastoma was found in children with an inborn chromosomal anomaly involving the partial loss of part of the long arm of chromosome 13. The long-term inhalation of benzene leads to chromosome aberrations and increases the susceptibility of persons so exposed to leukemia. Among the solid tumors of humans, meningioma and malignant lymphoma may be associated with specific chromosome aberrations. Malignant cell transformation may be triggered by the loss of a well-defined chromosome segment, but chromosome aberrations may be merely an accompanying phenomenon of oncogenesis that has no direct relation to it. The chromosome theory of oncogenesis is compatible with those for chemical, viral and immunological oncogenesis. (101 refs)

78-1822 **Possible Pathogenic Mechanisms in Aplastic Anemia.** (Eng) Boggs, D. R. (Dept. Medicine, Univ. Pittsburgh, Pittsburgh, PA, 15213); Boggs, S. S. *Transplant Proc* 10(1): 125-130; 1978.

Investigations of the production of idiopathic aplastic anemia suggest that different mechanisms are operable in different patients. However, since prolonged, stable hypoplasia may occur and only partial recovery is observed in many patients, a defective stem cell is probably the basis for the pathology. (9 refs)

78-1823 **Carcinoma in a Gastroenterostomy Stoma (Letter to Editor).** (Eng) Jones, S. M. (Univ. Dept. Surgery, Bristol Royal Infirmary, Bristol, England). *Br Med J* 1(6110): 443; 1978.

A review of a series of gastric carcinomas that occurred after surgery for benign conditions indicates that the area of the gastromosis is the most common site of cancer development. This contradicts a previous statement reporting that only a minority of these carcinomas have been restricted to the stoma. (6 refs)

78-1824 **Dysplasia: A Real Concept or a Misnomer?** (Eng) Koss, L. G. (Dept. Pathology, Albert Einstein Coll. Medicine, Montefiore Hosp. and Medical Center, 111 E. 210th St., Bronx, NY, 10467). *Obstet Gynecol* 51(3): 434-439; 1978.

Problems involved in classifying precancerous lesions of the epithelium of the uterine cervix are reviewed. The names given to these lesions, ranging from mild dysplasia to carcinoma in situ, do not necessarily reflect their true biologic potential in terms of disappearance, persistence, or progression. Their biologic behavior in tissue culture, ultrastructure, cytogenetic evidence, and studies of DNA content indicate that carcinoma in situ and dysplasia are biologically similar, if not identical. Because of the unreliability of an in situ or dysplastic diagnosis and the error possible with a cytologic diagnosis, extensive cytology studies are recommended, with colposcopy to be used at the first sign of abnormality. It is suggested that a single term such as cervical intraepithelial neoplasia (CIN) be adopted for all precancerous lesions of the uterine cervix. CIN Grade I could represent slight morphologic changes, and CIN Grade IV could represent classic carcinoma in situ. Such a system would eliminate the current chaotic interpretation of histological specimens. (33 refs)

78-1825 **Endometrial Sarcomas.** (Ita) Aimone, V. (Servizio Richerche Cliniche e Anatomia Patologica, Divisione Ostetrico-Ginecologica C, Ente Ospedaliero Provinciale Specializzato, Sant Anna di Torino, Turin, Italy); Torretta, G. M. *Minerva Ginecol* 29(9): 675-690; 1977.

Modification of the World Health Organization classification of uterine tumors is proposed. Malignant non-epithelial tumors (Group IV) should include leiomyosarcoma, endometrial (stromal) sarcoma, and stromal endolymphatic myositis. Mixed tumors (Group V) should include mixed mesenchymal tumors and carcinosarcoma. (102 refs)

78-1826 **Dietary Carcinogens.** (Ger) Sailer, D. (Abteilung für Stoffwechsel und Ernährung, Medizinische Universitäts-Klinik Erlangen, Krankenhausstrasse 12, D-8520 Erlangen, W. Germany). *Fortschr Med* 96(9): 446-449; 1978.

Studies of dietary carcinogens (polycyclic aromatic hydrocarbons, nitrosamines, and mycotoxins) are reviewed. Benzo(a)pyrene, a product of incomplete combustion, is found throughout the environment, especially in urban and industrial areas and near highways. It also occurs in air, plants, drinking water, fish, and in smoked, pickled, and roasted meat. Nitrosamines occur in certain foods, and they are also synthesized in the stomach. The synthesis is catalyzed by thiocyanate, which is present in high concentrations in the saliva, especially in that of smokers. Epidemiological studies revealed a correlation between nitrate and nitrite levels in food and the incidence of human tumors. A relationship was found between the incidence of liver tumors in humans and dietary aflatoxin intake. The use of alcohol, especially when com-



bined with smoking, causes a considerable increase in the risk of cancer of the mouth, larynx, and esophagus, which is possibly due to the characteristic vitamin B deficiency in alcoholics. Relationships were also found between vitamin A deficiency and cancer of the cervix and between obesity and certain tumors. The increased incidence of gastric cancer among Japanese may be due to the consumption of rice polished with talc, a potential carcinogen. Talc crystals were found in tumor tissues from 6/7 gastric cancer patients in Japan. (35 refs)

- 78-1827 **Gastrointestinal Cancer: Epidemiology and Experimental Studies.** (Eng) Jansson, B. (Houston, TX, 77030); Jacobs, M. M.; Griffin, A. C. *Adv Exp Med Biol* 91: 305-322; 1977.

Epidemiological and experimental data on the anticarcinogenic properties of selenium are reviewed. The hypothesis of a negative correlation between the prevalence of Se and colorectal mortality rates was contradicted in a study of both parameters in the northeastern U.S. where the rate of colorectal cancer is high. There was a linear relationship between Se concentration and these mortality rates. Another study revealed a positive correlation between colon and rectal cancer and the amount of meat and sugar in the diet; a negative correlation was observed with the amount of cereals and fish (foods rich in Se). The opposite was true for stomach and liver cancer. It is not known if Se protects against colorectal cancer and contributes to the development of stomach and liver cancer, or if other factors are involved. Data from experiments with rats, mutagenesis assays, and assays with cultured human lymphocytes indicating a cancer-inhibiting effect of Se are also presented. (24 refs.)

- 78-1828 **Colon Cancer: Its Epidemiology and Experimental Production.** (Eng) Weisburger, J. H. (Naylor Dana Inst., American Health Foundation, Valhalla, NY 10595); Reddy, B. S.; Wynder, E. L. *Cancer (Suppl)* 40(5): 2414-2420; 1977.

Worldwide incidence patterns indicate that colon cancer is an environmental disease. Japan, Africa, and Central and South America have a low incidence, but the US and other Western countries have a high incidence. A high intake of dietary fat appears to be associated with a higher risk for colorectal cancer. Populations on a high-fat diet have higher levels of fecal bile acids and cholesterol metabolites and higher levels of total fecal anaerobic bacteria and bacterial  $\beta$ -glucuronidase activity. In experimental animals, colorectal cancer has been induced with cycasin, 1,2-dimethylhydrazine, azoxymethane, methylazoxymethanol, N-methylnitrosourea, N-methyl-N'-nitro-N-nitrosoguanidine, 3-methyl-4-aminobiphenyl and its analog,

3-methyl-2-aminonaphthalene, and 3-methylcholanthrene. Animals given DMH and maintained on a high-fat diet developed more colon tumors than those maintained on a low-fat diet. Animals on the high-fat diet excreted more neutral steroids and bile acids than controls. In other experiments, bile acids promote colon carcinogenesis in mice. (44 refs.)

- 78-1829 **Diet and Cancer of the Colon.** (Eng) Wynder, E. L. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY); Reddy, B. S. *Curr Concepts Nutr* 6: 55-71; 1977.

The relationship between nutrition and the etiology of colorectal cancer is examined. Diet, particularly a high-fat diet, is a major etiologic factor, although not the sole factor, in colorectal cancer development. Demographic studies indicate that the incidence of colorectal cancer in a population is related principally to meat and fat consumption. Other studies indicate that deficiency of dietary fiber, transit time of the stool, and dietary excess of refined sugars are not important factors in the etiology of large bowel cancer as had been suggested previously. Conversion of cholesterol and  $\Delta^5$ -cholestenol to dehydrocholesterol, which are normally found in colon contents and mucosa, by electrolytic oxidation to reactive metabolites capable of interacting with nucleophiles and acting as carcinogens may be an important step in colon carcinogenesis. Dietary fat or meat changes the concentration of fecal bile acids and cholesterol metabolites and also the metabolic activity of colon bacteria, which may produce tumorigenic compounds from bile acids. These bile acids as colon tumor promoters, but not complete carcinogens. The effect of bile acids in colon carcinogenesis has received substantial support from animal studies: these studies also provide some support for the possible role of dietary fat in colorectal cancer. Human metabolic studies indicate that high dietary fat affects the metabolic activity of intestinal bacteria as well as the levels of certain bile acids and cholesterol metabolites that can act as colon tumor promoters. (51 refs.)

- 78-1830 **The Upper Digestive Tract and Alcohol.** (C) Bode, J. C. (Medizinische Universitätsklinik, Mannkopfstrasse 1, D-3550 Marburg/Lahn, W. Germany); Menge, H. *Internist (Berlin)* 19(2): 116-122; 1978.

Epidemiological studies show a statistically significant correlation between total alcohol consumption and the frequency of carcinomas of the buccal cavity and pharynx. There is a probable relationship between alcohol abuse and esophageal carcinoma. (33 refs)

- 78-1831 **Dietary Fiber and Fiber Supplements in the Therapy of Gastrointestinal Disorders.** (I)



er, J. T. (Francis Stearns Nutrition Center, New England Medical Center Hosp., 185 Harrison Ave., Boston, MA, 02111); Goldin, B.; Gorbach, S.; Patterson, J. *Am J Hosp Med* 35(3): 278-287; 1978.

role of dietary fiber in gastrointestinal disorders is reviewed with emphasis on the source, composition, and properties of the fiber. The major hypotheses linking diet with cancer are that: differences in incidence are associated with variations in the fiber content of the diet; differences in incidence are associated with the type of lipid and/or protein in the diet; and toxic substances in the diet cause increased cancer development. (53 refs)

78-1832 **Endoecology and Cancer.** (Eng) DeCarvalho, S. (Belmont Medical Clinic, Bellflower, CA, 90610). *J Clin Hematol Oncol* 8(1): 11-31; 1978.

role of endoecology in cancer induction and treatment is reviewed. Endoecology comprises internal chemical environment, homeostasis and immunosurveillance of an organism. Carcinogens disrupt the host endoecology and thus cause cancer, which disrupts the endoecology by its demands for essential nutrients such as iron, glucose, oxygen, and amino acid. Immunosuppressant peptides produced by cancer and host cells as well as lipoprotein-carried cholesterol enter into cancer-killing macrophages favor cancer growth. There is evidence for some sort of cytological intelligence in the immune response induced in the host by cancer cells. (82 refs)

78-1833 **The Environment of Man in the Light of a New Theory of Medicine.** (Ger) Schaefer, H. (Physiologisches Institut der Universität, Im Neuenheimer Feld 326, D-6900 Heidelberg 1, W. Germany). *Wochenschr* 55(24): 1197-1207; 1977.

natural environment for man would be one in which his life is in equilibrium with his development. Even natural environments contain certain risk factors. Epidemiologic studies are often difficult to perform, and the results may be uncertain or indirect; they are best explained by physiological and psychological models. The inadequacies of epidemiologic studies can be demonstrated by examples of cancer due to smoking or to the use of artificial fertilizers. Epidemiological research indicates that disease appears as a result of disturbed conditions of existence. The few noxious substances that seem to elicit disease to a measurable degree occur in industry and agriculture and in automobile exhaust. Deaths due to heart disease, liver cirrhosis, and carcinomas of the lungs and stomach are increasing rapidly. There is a hierarchy of risk factors, in which the first causes of a disease are either genetic or extrinsic; social factors may be the most prominent external causes. (28 refs)

78-1834 **Transplacental Carcinogenesis.** (Rus) Napalkov, N. P. (N. N. Petrov Inst. Oncology, Leningrad, USSR). *Vestn Akad Med Nauk SSSR* (10): 14-19; 1977.

Literature pertaining to transplacental carcinogenesis is reviewed. At the end of 1976, one human tumor registry contained data on 213 cases of transplacentally induced clear cell adenocarcinoma of the vagina and 120 cases of carcinoma of the cervix uteri. These tumors occurred in subjects aged 7-27 yr; approx half of the patients survived > 5 yr after diagnosis. Numerous experimental studies revealed that a congenital malformation per se does not cause tumor growth and that teratogenesis and carcinogenesis might result independently from a common etiologic factor. (39 refs.)

78-1835 **Geographic Clues to High-Risk Groups in Cancer.** (Eng) Fraumeni, J. F. (Environmental Epidemiology Branch, NCI, NIH, Bethesda, MD, 20014). *Cancer Bull* 29(6): 191-194; 1977.

The mapping of cancer mortality by county and then correlating the data with demographic and environmental data allow the formulation of hypotheses for the causes of cancer. These maps indicate that in men and women, the death rates for all cancers are highest in the northeastern section of the country and in southern Louisiana. Colon cancer mortality is highest in the northeast and lowest in the south. There is also a high death rate in rural farming communities in southeastern Nebraska. Persons who migrate from low-risk to high-risk areas and vice versa take on the risk feature of the area to which they migrate. Deaths from stomach cancer are clustered in the north-central and southwestern areas of the country for whites and in southern Louisiana for blacks. The highest rates for lung cancer are found along the Gulf of Mexico and along the southeastern Atlantic coast. Rates are also high in the northeast and around metropolitan areas. Counties with paper, chemical, petroleum, shipbuilding, and nonferrous smelting industries had the highest mortality. Bladder cancer mortality for men is high in New Jersey, in urban areas along the Great Lakes, and in rural New York and New England; for women, the rates are highest in northern New England. Breast cancer parallels the distribution of colon cancer. Oropharyngeal cancer in men is highest in the urban northeast, consistent with patterns of tobacco smoking and alcohol consumption, but oral cancer in women is highest in the south. Snuff is a suspected etiologic agent in the latter area. Rates for esophageal cancer parallel those for oral cancer. (18 refs)

78-1836 **Geographic Distribution of Head and Neck Cancers in the United States.** (Eng) Fraumeni, J. F. (C307 Landow Bldg., 7910 Woodmont Ave., Bethesda, MD 20014). In: *Head and Neck Cancer. State of the Art*



*Conference. February 16, 17 and 18, 1976. (St. Louis, MO: Laryngoscope): Vol. 88, No. 1, Part 2, Suppl. 8, pp. 40-44; 1978.*

The total number of cancer deaths between 1950 and 1969 and aged-adjusted rates according to sex and race were determined for all US counties (except those in Alaska and Hawaii), and the incidence of various cancers was plotted on maps. Tumors of the nasal cavity and sinuses show some clustering in men in Texas and Louisiana. Rates of this cancer are significantly higher among men and women in counties with high concentrations of chemical industries. Among men, cancer of the oropharynx occurs excessively in the urban northeast and is consistent with tobacco and alcohol consumption. For women, this cancer predominates in the southeast, and it is associated with the use of snuff. Salivary gland cancer is clustered in men in the Florida panhandle, Alabama, Mississippi, and Louisiana. However, a separate analysis has shown that the highest rates occur in Alaskan Eskimos. Nasopharyngeal cancer in men shows clustering in Maryland and the coastal areas of North Carolina. People in areas with high concentrations of chemical industries and high rate of nasopharyngeal carcinoma are also prone to bladder cancer. Esophageal cancer is clustered in the northeast in men and the southeast in women. Laryngeal cancer is common in the northeast, particularly around New York City, and along the southeast Atlantic coast and Gulf Coast. There is a high mortality for thyroid cancer in the north central area and the Rocky Mountain states. (18 refs.)

**78-1837 Epidemiology of Head and Neck Cancer.** (Eng) Rothman, K. J. (Dept. Epidemiology, Harvard Univ. Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115). *Laryngoscope* 88(3): 435-438; 1978.

Epidemiological factors associated with cancers of the lung, larynx, esophagus, and mouth are reviewed. Environmental contaminants such as asbestos, radon gas, arsenic, chromium, coal products, iron oxide, mustard gas, nickel, and petroleum account for many lung cancers, but the major environmental cause is cigarette smoking (80%-90% of all cases). The risk of lung cancer is positively related to the number of cigarettes smoked per day, extent of inhalation, and number of smoking years. Studies have suggested that aryl hydrocarbon hydroxylase inducibility may be a susceptibility factor for the action of tobacco smoke. Laryngeal cancer is also related to cigarette smoking, but cigar and pipe smoking and alcohol consumption are also associated with the disease. Recent data suggest that the risks associated with smoking and alcohol consumption are synergistic. Cancer of the esophagus has certain geographic variations, but the incidence in the US appears to be associated with alcohol consumption. It is possible that contaminants in the alcoholic beverage, and not ethanol per se, play a role in cancer development. Oral and pharyngeal cancers are associated with alcohol and tobacco use, and it is estimated that these two risk factors combined account for

75% of all oral cavity cancers in US men. A synergistic action may also exist. It is estimated that already identified factors account for >90% of new head and neck cancer cases and that tobacco alone is related to approx 80% of all the cancers in the US. (10 refs)

**78-1838 Consequences of Childhood Irradiation.** (Eng) Steinfeld, A. D. (Malcolm Grow USAF Medical Center, Washington, DC). *Am Fam Physician* 17(3): 181; 1978.

In evaluating patients who were treated with therapeutic doses of ionizing radiation as children, special attention must be focused on the indications for treatment; length, number, and frequency of treatments; and the radiation type and dose. The data indicate that radiation-induced tumors have long periods of 5-30 yr, but this varies with the dose, type of radiation, and type of tumor. A management profile for patients with a history of head and neck irradiation is provided. (10 refs)

**78-1839 Experimental Research on Thyroid Cancer. Review of Literature.** (Eng) Nataf, B. M. (Service de Radiobiologie clinique, INSERM, CNRS, Institut Gustave Roussy, 16 bis avenue Paul Vaillant-Couturier, F94 Villejuif, France). *Ann Radiol (Paris)* 20(8): 703-714; 1978.

Research on the various suspected etiological agents associated with thyroid cancer is reviewed. An iodine-deficient diet can induce thyroid cancer in animals. A prolonged stimulation of thyroid-stimulating hormone (TSH) would be the local factor responsible for both the hyperplasia and the tumor formation. Chronic stimulation of the thyroid with TSH probably lead to carcinogenesis in man. The role of head and/or neck irradiation in childhood in the etiology of thyroid cancer has been clearly established. There is also evidence that irradiation can cause thyroid cancer in animals. Although benign and malignant tumors of the thyroid are three to four times as common in women as in men, conflicting results make it difficult to define the role played by hormones in the formation and development of experimental tumors of the thyroid. Immunological studies have not clarified whether antigen deficiency plays a role in the growth and development of thyroid tumors. Numerous biochemical abnormalities have been found in thyroid cancer that involve the synthesis and iodination of thyroglobulin, as well as the initial steps of hormone synthesis, iodide trapping, and/or enzymatic processes leading to the oxidation and metabolism of iodide, and the responsiveness of the cell to TSH. (214 refs)

**78-1840 Patterns of Human Thyroid Parenchymal Reaction Following Low-dose Childhood Irradiation.**



(g) Spitalnik, P. F. (Dept. Pathology, Pritzker Sch. Medicine, Univ. Chicago, 950 E. 59th St., Chicago, IL, 60637); Maus, F. H. *Cancer* 41(3): 1098-1105; 1978.

The histologic changes in the thyroid glands of 68 patients (aged 13-57 yr) 34 nonirradiated with a history of head and neck irradiation in childhood were compared with those in nonirradiated autopsy cases (aged 19-45 yr). The sex ratio of the two groups was approx the same. In most of the irradiated patients, the exact thyroid dosage could not be determined, but it was <1,000 rads. The thyroid glands of the irradiated patients showed moderate to severe focal hyperplasia (88%), single or multiple adenomas or adenomatous hyperplastic nodules (51%), chronic lymphocytic thyroiditis (42%), colloid nodules (51%), oxyphile changes (42%), mild atrophy (25%), and well-differentiated papillary, follicular, or mixed thyroid carcinomas averaging 1.6 cm in diameter (17%). Three small carcinomas were of the sclerosing type. The nonirradiated thyroids showed colloid nodule formation (17%), focal hyperplasia (17%), and adenomatous hyperplasia (6%). It is suggested that radiation-induced focal hyperplasia may represent a premalignant change in thyroid parenchyma. On the basis of these and literature results, it appears that the induction of thyroid carcinoma requires not only radiation damage to the genetic material, but also a long stimulus toward hyperplasia and increased parenchymal cell activity. (22 refs)

78-1841 **Anxieties and Fears about Plutonium and Other Radionuclides (Letter to Editor).** (Eng) Mole, H. (MRC Radiobiology Unit, Harwell, Didcot, Oxon, England). *Br Med J* 1(6104): 46; 1978.

Plutonium and other  $\alpha$ -emitting radionuclides can induce cancer in workers exposed industrially and in the general population through environmental exposure. Compared with cancer induction, hereditary damage is not an important consequence of the radiation. The theory that a doubling of the human mutation rate could imperil survival has not been proven by experimental and epidemiological data. (9 refs)

78-1842 **DNA Repair.** (Eng) Lehmann, A. R. (MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, England); Bridges, B. A. *Essays Biochem* 13: 71-9; 1977.

A review of RNA repair literature indicates that evidence for DNA damage in carcinogenesis comes from studies with UV light-induced pyrimidine dimers, the demonstration that most carcinogens are either DNA-damaging or are converted to such species, studies of the removal of N-ethyl-N-nitrosourea-induced O-6-ethylguanine residues in CNS DNA, and studies of xeroderma pigmentosum patients. Various methods of DNA repair are also reviewed. (245 refs)

78-1843 **Immunity, Herpes Simplex Virus, and Cervical Carcinoma.** (Eng) Mumford, D. M. (Meredith Mosle Lab. Cancer Res., Dept. Obstetrics and Gynecology, Baylor Coll. Medicine, Houston, TX, 77030); Kaufman, R. H.; McCormick, N. *Surg Clin North Am* 58(1): 39-54; 1978.

The major immunological findings associated with herpes simplex virus (HSV) and cervical cancer are reviewed. Studies have indicated that women likely to contact one venereal disease, such as genital herpes, are more likely to acquire cervical cancer; furthermore, more neutralizing antibodies to herpesvirus are found in women with invasive cancer than in controls. These findings suggest an association between viral infection and cervical cancer, and this holds when patients are matched for age, race, socioeconomic factors, and sexually related factors. HSV infections develop at an earlier age than carcinoma of the cervix, and the mean age of women with HSV infections dysplasia, carcinoma in situ, and invasive carcinoma is 20, 25, 31, and 48 yr, respectively. Antibodies to HSV are present in a greater number of cancer patients than controls. Furthermore, antisera prepared against semipurified HSV-2 in guinea pigs reacts with a soluble membrane antigen from patients with vaginal, vulvar, and cervical cancer. The background evidence for immune factors in cervical cancer patients, changes in immune reactivity in these patients, and other immunologic facets of cervical cancer (histocompatibility antigen B-12 and carcinoembryonic antigen association) are also reviewed. (66 refs)

78-1844 **Histocompatibility (HLA) Antigens and Disease.** (Rus) Tananov, A. T. (Lab. Immunohematology, Central Inst. Hematology and Blood Transfusion, Moscow, USSR). *Probl Gematol Pereliv Krovi* 23(3): 45-50; 1978.

The associations between histocompatibility (HLA) antigens and various diseases are reviewed. The incidence of antigen A2 is significantly increased in patients with acute leukemia; however, leukemia patients with antigen A9 have an increased survival time. Myeloma patients have a three- to four-fold higher frequency of antigens A28 and B27. Various other antigens of the HLA system were found to be associated with cervical carcinoma, malignant melanoma, lymphosarcoma, and cancer of the stomach. (68 refs)

78-1845 **Malignancies of the Urinary Tract and Their Relation to Analgesic Abuse.** (Eng) Bengtsson, U. (Dept. Nephrology, Univ. Hosp., Lund, Sweden); Johansson, S.; Angervall, L. *Kidney Int* 13(7): 107-113; 1978.

The literature on the association between analgesic abuse and urinary tract malignancies is reviewed. Over 100 cases of epithelial tumor of the renal pelvis or bladder have been reported in abusers of phenacetin-containing drugs; many patients had



a preexisting nephropathy with renal papillary necrosis. Study of a representative sample of 38 of these patients indicated a mean phenacetin consumption of 9.1 kg over 17 yr; the time to tumor induction was 22 yr. Multiple urinary tract tumors were common. The clinical and pathological findings for these tumors are described. Animal experiments with long-term phenacetin feeding have resulted in a high degree of papillary epithelial hyperplasia. Phenacetin, an aromatic amide with N-hydroxylated metabolites, is closely related to amines known to cause bladder cancer. Furthermore, the data on the consumption and tumor induction times are similar for occupational bladder cancer and renal pelvic cancer resulting from analgesic abuse. Further investigations are needed to rule out a carcinogenic effect by other components in analgesic compounds. (50 refs)

**78-1846 Effects of Cancer Treatment on Individual and Generational Genetics.** (Eng) Bender, R. A. (Medicine Branch, NCI, Building 10, Room 12N226, 9000 Rockville Pike, Bethesda, MD, 20014); Young, R. C. *Semin Oncol* 5(1): 47-56; 1978.

The risks of second malignancies and genetic disorders in patients being treated for cancer are reviewed. Literature data indicate that individuals who survive for long periods after treatment with either x-rays or chemotherapy are at an increased risk for the development of a second cancer. Furthermore, combined chemotherapeutic and radiation treatment may exert a synergistic effect. The precise mechanisms of oncogenesis following radiotherapy and/or chemotherapy are unknown. Radiotherapy and single or combination chemotherapy can produce sterility in both men and women. The radiotherapeutic effects appear to be dose- and time-dependent, but the chemotherapeutic effects are largely dose-dependent. Patients who have remained fertile have sired or borne normal children, but the long-term genetic effects are unclear. Pregnancy studies have indicated that x-rays and chemotherapeutic agents exert their highest teratogenic potential during the first trimester of pregnancy. Genetic counseling is warranted both for pregnant patients about to undergo treatment and for treated patients who desire more children. (75 refs)

**78-1847 The Hygiene Standard for Chrysotile Asbestos.** (Eng) Peto, J. (D.H.S.S. Cancer Epidemiology and Clinical Trials Unit, 9 Keble Road, Oxford, England). *Lancet* 1(8062): 484-489; 1978.

Previous studies, including the 1966 analysis by the British Occupational Hygiene Society, on which the current 2 fibers/cm<sup>3</sup> hygiene standard for chrysotile asbestos is based, may have underestimated the risk of morbidity or mortality following exposure to low levels of asbestos dust. Accurate dose-response data at levels below 2 fibers/cm<sup>3</sup> are unlikely to be

available for the foreseeable future, and the biologically plausible assumption that excess cancer mortality is proportional to the dust level should be provisionally accepted. In a new study, the number of deaths from bronchial carcinoma, pleural mesothelioma, and other respiratory diseases among male asbestos textile factory workers were compared with the expected numbers based on national rates. There was a substantial excess due to cancer and respiratory disease > 25 yr after first exposure (35 observed; 15.74 expected). Fourteen deaths (6.57 expected) were due to bronchial carcinoma, 17 (9.1 expected) to nonmalignant respiratory disease, and 4 to pleural mesothelioma. Peritoneal mesothelioma is usually due to crocidolite (blue asbestos) or other amphiboles, but exposure to chrysotile (white asbestos) alone may lead to a substantial risk of pleural mesothelioma. If excess mortality from asbestos-related disease is proportional to the dust level for each cause, then 10% of male asbestos workers might eventually die of asbestos-induced disease after 50 yr exposure to 2 fibers/cm<sup>3</sup>. (18 refs)

**78-1848 An Overview of the Canadian Asbestos Problem.** (Eng) Charlebois, C. T. (Science Council of Canada, Canada); Rivest, F.; Nichols, A. *Chem Canada* 30(3): 19-38; 1978.

The physical properties, distribution, production, use, disposal, and health hazards of asbestos are reviewed. Asbestos is a naturally occurring fiber that is used in construction, friction materials, and as a fire retardant. Studies of its health effects have indicated associations with several diseases. Asbestosis leads to airway obstruction and replacement of the lung alveoli by dense fibrous tissue; it may lead to pulmonary hypertension and cardiac arrest. It also acts as a lung carcinogen, with a latent interval of 20-30 yr between initiation of exposure and onset of symptoms. Autopsy studies indicate that 15% of all persons with asbestosis have bronchial cancer. Asbestos exposure has also been associated with tumors of the pleura and peritoneum (mesotheliomas). It may play an etiologic role in tumors of the gastrointestinal system, ovaries, and larynx. The existing regulations and legislation on asbestos exposure are reviewed. (84 refs)

**78-1849 2,4-Diaminoanisole in Hair and Fur Dyes.** (Eng) Stein, H. P. (Natl. Inst. Occupational Safety and Health, 5600 Fishers Lane, Rockville, MD, 20857); Balman, L. J.; Parker, J. C.; Leidel, N. A.; Thomas, A. W.; Woolf, B. S.; Baier, E. J. *Am Ind Hyg Assoc J* 39(3): A-17-A-21; 1978.

The carcinogenic effect of 2,4-diaminoanisole and its salts are reviewed based on experimental and epidemiological data from the National Institute for Occupational Safety and Health. Fifty male and 50 female Fischer 344 rats were fed 0.05% or 0.12% 2,4-diaminoanisole sulfate for 78 wk. T



were then observed an additional 26 wk. A significant excess of thyroid and skin cancer was noted in the high-dose group of both sexes. Fifty male and 50 female B6C3F1 mice were fed doses of 0.12% or 0.24%. After 78 wk, the mice were observed for an additional 13 wk. A significant excess of thyroid cancer was noted in mice exposed to the high dose, and an excess of lymphatic cancer was present in low-dose mice. Two human epidemiologic studies have found a significant excess of cancer of the digestive organs, respiratory system, trachea, bronchus, lung, breast, and genital organs among cosmetologists. It is suggested that 2,4-diaminoanisole and its salts be handled in the workplace as if they were known carcinogens. (10 refs)

**78-1850 International Workshop on Toxicology of Benzene, Paris: 9th - 11th November 1976.** (Eng) Chahut, R. (Laboratoire de Toxicologie et d'Hygiene Industrielle, Faculte des Sciences Pharmaceutiques et Biologiques, Paris Luxembourg, 4 avenue de l'Observatoire, Paris VI, France); Murray, R. *Int Arch Occup Environ Health* 41(1): 1-16; 1978.

A review of the toxic effects of benzene, based on papers presented at an international workshop on this subject, is presented. The myelotoxic effects of benzene have been recognized over a long period, but recent evidence has indicated a possible leukemogenic effect in humans. Chromosome studies, however, have not been able to establish a dose-effect relationship for benzene-induced aberrations. Data on benzene metabolism are also reviewed. (4 refs)

**78-1851 Experimental Data on Metabolism and Biological Activity of Benzidine Uptake in Humans.** (Pol) Wiczeorek, H. (Zaklad Biochemii, Instytutu Medycyny, UL. Teresy 8, 90-950 Lodz, Poland); Trojanowska, B. *Med Pr* 28(5): 403-409; 1977.

The biological activity and metabolism of benzidine are reviewed. Papillomas of the urinary bladder were observed in rats exposed to benzidine. Monoacetylbenzidine, diacetylbenzidine, 3-hydroxybenzidine ether sulfate, 3-hydroxybenzidine glucuronate, N-hydroxyacetylaminobenzidine, and 3,3'-dihydroxybenzidine were identified as benzidine metabolites in the human body. (45 refs)

**78-1852 The Metabolism and Toxicity of Safrole and Estragole.** (Eng.) Rostron, C. (No affiliation given). *Food Cosmet Toxicol* 15(6): 645-646; 1977.

Studies in rats and mice and limited studies in humans showed that the carcinogenic metabolites of safrole and es-

tragole, two related naturally occurring flavorings, are produced only at high doses. At high doses, a primary metabolic pathway may become saturated, or it is possible that at low doses carcinogenic metabolites are produced too slowly and eliminated too rapidly for any biological effects to be exerted. The ultimate carcinogenic metabolites of safrole and estragole may be 1'-acetoxysafrole and 1'-hydroxyestragole. (no refs)

**78-1853 Tetrachloroethylene (Perchloroethylene).** (Eng) Parker, J. C. (Natl. Inst. Occupational Safety and Health, 5600 Fishers Lane, Rockville, MD, 20857); Bahlman, L. J.; Leidel, N. A.; Stein, H. P.; Thomas, A. W.; Wolf, B. S.; Baier, E. J. *Am Ind Hyg Assoc J* 39(3): A-23-A-29; 1978.

Animal and human data on the toxicity of tetrachloroethylene (perchloroethylene) are reviewed. Force feeding of the compound to B6C3F1 mice at doses of 536 or 1,072 mg/kg/day for males and 386 or 772 mg/kg/day for females for 78 wk resulted in hepatocellular carcinoma in > 50% of the males and 40% of the females. Studies in which the compound was inhaled did not provide sufficient data for evaluation of carcinogenicity. Tetrachloroethylene has been shown to cause liver and kidney damage, CNS depression, skin irritation, and cardiac depression in animals; it is also teratogenic in rats and mice. Human data indicate that it is toxic to the liver and kidneys, it is an eye irritant, and it can cause burns, blistering, and erythema of the skin; CNS depression has also been observed. This compound is usually absorbed through the lungs, but it can be absorbed from the intestines if ingested. It is deposited in the body fat and has an estimated biological half-life of 6 days in humans. It is suggested that this compound be handled in the workplace as if it were a human carcinogen. (14 refs)

**78-1854 Cancer of the Upper Respiratory Tract in Woodworkers.** (Fre) Sporck, J. (Universite Libre de Bruxelles, Brussels, Belgium). *Brux Med* 58(1): 35-41; 1978.

The literature on the epidemiology of carcinoma of the nasal cavity and accessory sinuses in woodworkers is reviewed. These tumors are usually adenocarcinomas, and they are 1,000 times more frequent in woodworkers than in workers in other industries. Workers in tanning and shoe industries are also susceptible to the development of such tumors. The average duration of exposure is 30 yr, and diagnosis is made as late as 12 yr after initial symptoms. The majority of patients who die of this lesion are about 65 yr old, and no deaths occur before 40 yr. The tannins in the wood may be the carcinogens;



however, the incidence of the nasal cancers does not appear to be related to the tannin concentration, which varies in different wood species. Although tannin is a factor, the more important factor appears to be exposure to the sawdust, and workers from the period 1920-1945 when shop standards for ventilation were less strict are at a higher risk. (89 refs)

- 78-1855 **Vitamin K and Chemical Carcinogenesis (Letter to Editor).** (Eng) Hadler, H. I. (Dept. Chemistry and Biochemistry, Southern Illinois Univ., Carbondale, IL, 62901); Cao, T. M. *Lancet* 1(8060): 397; 1978.

The carcinogen 4-nitroquinoline 1-oxide and its metabolite 4-hydroxyaminoquinoline 1-oxide release the rotenone inhibition of the NADH branch of the respiratory chain in mitochondria isolated from rat liver, a finding previously found for vitamin K. It is suggested that malignancy could result from the leakage of mitochondrial genes that then become incorporated into nuclear DNA. Oncogenic genes are thus not unique to oncoviruses. (9 refs)

- 78-1856 **Evolution, Environment and Cancer.** (Eng) Ors, Y. (Dept. History Medicine, Ankara Medical Faculty, Sıhhiye, Ankara, Turkey). *Proc R Soc Med* 70(11): 753-754; 1977.

A study of pathopaleontological records indicates that cancer, like other diseases, has been with man throughout history. Although multiple factors may influence tumor development, oncogenic viruses appear to be the key factor in the process. These viruses may be transmitted both horizontally and vertically, linking evolution with viral infection. A genetic mechanism in cancer could reflect a viral and environmental factor at work. (19 refs.)

- 78-1857 **Diethylstilbestrol: Twenty-five Years Later.** (Eng) Ryan, K. J. (Boston Hosp. Women, Boston, MA, 02115). *N Engl J Med* 298(14): 794-795; 1978.

A slight, nonsignificant excess of breast cancer has been detected in women 25 yr after exposure to  $\leq 12$  g of diethylstilbestrol (DES) for 15-20 wk during pregnancy. The exposed women had an earlier onset of disease and an excess number of deaths, compared with a control group. Since this and other studies have suggested that estrogens may cause or predispose a woman to breast cancer, women exposed to estrogens in the past should undergo careful surveillance. (9 refs)

- 78-1858 **The Biologic Aspects of Cancer of the Breast: A Challenge.** (Eng) Copeland, M. M. (U. Cancer Foundation, 6723 Bertner Ave., Houston, TX 77030). *J Am Geriatr Soc* 26(3): 97-107; 1978.

A general review of breast cancer is presented. The incidence rate for breast cancer in women is nearly twice that for the next most common malignant disease found in both men and women. The percentage of patients with localized disease gradually increased but appears to be reaching a plateau. High-risk factors and methods of early detection are outlined. (77 refs)

- 78-1859 **Cigarette Smoking and Reactions to Air Pollutants.** (Eng) Shephard, R. J. (Dept. Preventive Medicine and Biostatistics, Faculty Medicine, Univ. Toronto, Toronto, Ontario M5S 1A8, Canada). *Can Med Assoc J* 118(4): 379-381, 383, 392; 1978.

Cigarette smoking can augment the toxicity of air pollutants by increasing the pollutant burden and the degree of irritation, altering ventilatory patterns and mucosal characteristics, depressing ciliary functions, and increasing the risk of specific allergic reactions. Both short- and long-term cigarette smoking can be cocarcinogenic with air pollutants. (8 refs)

- 78-1860 **Tumor Virus Expression During Mammalian Embryogenesis.** (Eng) Jaenisch, R. (Heinrich Pette-Institut für Experimentelle Virologie und Immunologie, Hamburg, W. Germany); Berns, A. In: *Concepts in Mammalian Embryogenesis*. Sherman, M. I., ed. (Cambridge, MA: MIT Press); Cell Monograph Series No. 1, 404 pp.; 267-319; 1977.

A review of the potential importance of tumor virus expression during embryogenesis is presented based on data obtained with murine systems. Specific topics include the effects of exogenous tumor viruses and the expression of endogenous viruses during embryogenesis. The viral proteins p30 and gp70 may play an important role in embryogenesis, but they are not expressed in all types of mice at the same stage of development. Strains such as BALB/c have little or no detectable virus proteins during embryonic or adult life, C57BL/6 expresses high gp70 but little or no p30, NZB has high levels of gp70 and moderate levels of p30 during embryonic and adult life, and AKR mice have little or no detectable virus proteins during embryogenesis, but they produce high levels of infectious virus later in life. The different viruses may be incorporated in specific genomes that are expressed only



tain times during development. Thus, a virus that causes most tumors may be incorporated in a breast-related genome and expressed only during breast development and regression. It is also possible that the viruses are located in specific chromosomal loci that are activated by hormones in certain organs. Whether activated viruses play important functional roles during embryogenesis is unknown. (138 refs)

**1861 RNA-Tumour-Virus Genes and Transforming Genes: Patterns of Transmission.** (Eng) Todaro, J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20814). *Br J Cancer* 37(2): 139-158; 1978.

A review of the association between RNA tumor virus genes and cancer is presented. These genes are contained in the chromosomal DNA of most vertebrates, and they may be transmitted vertically from parent to progeny as well as horizontally, as infectious particles. Their activation may be part of the means by which RNA tumor viruses produce cancer. Characterization of the viral genes has indicated that the envelope glycoprotein interacts with specific membrane receptors on the cell surfaces and that the major phosphoprotein binds to specific viral RNA sequences. C-type viral gene sequences have evolved as the species have evolved, and they have been transferred between distantly related species under natural conditions. The presence of genetically transmitted viral genes in several vertebrate species and the evidence that they may provide normal functions beneficial to the species are trying them suggest that the potential to cause cancer is a pathological manifestation of a normal physiological process. (80 refs)

**1862 HR-T Mutants of Polyoma Virus.** (Eng) Benjamin, T. L. (Dept. Pathology, Harvard Medical School, 25 Shattuck St., Boston, MA, 02115). *Miami Winter Conference* 14: 73-85; 1977.

Current knowledge of the function of the polyoma virus host range *hr-t* mutants and its relation to that of the temperature-sensitive *ts-a* mutants are reviewed. *Hr-t* mutants differ from wild-type polyoma virus in two important respects: they have a reduced cell range and they have lost the ability to transform cells. Tests for complementation between *hr-t* mutants and various *ts* mutants were performed by doubly infecting normal 3T3 cells at 39°C. The results indicated that the *hr-t* group complements with, and is therefore functional, different from, all known classes of *ts* mutants. Mapping experiments with three *hr-t* mutants indicated that the mutants were rescued by Hpa-II and Hind-III fragment four from the proximal (5') end of the early region. Hind-III cleavage of polyoma DNA separated the regions in which the *ts-a* and *hr-t* mutants mapped. *Ts-a* mutants produce a thermolabile T antigen and *hr-t* mutants produce an immunoreactive

T antigen in nonpermissive cells, but it is not known if the *hr-t* portion of the early region codes for a protein distinct from T antigen. The results are discussed in terms of a model that suggests that the *hr-t* viral gene is a regulatory gene affecting the pattern of expression of cellular genes. (23 refs)

**78-1863 Role of Viral Agents in the Etiology of Hemoblastosis in Primates.** (Rus) Yakovleva, L. A. (Inst. Experimental Pathology and Therapy, Sukhumi, USSR); Lapin, B. A.; Indzhiya, L. V.; Voevodin, A. F.; Agrba, V. Z.; Diyatchenko, A. G. *Vestn Akad Med Nauk SSSR* (8): 80-88; 1977.

Literature on the possible role of viruses in the etiology of hemoblastosis (HB) in primates is reviewed. Characteristic features of HB in primates are a fluctuating clinical course (alternate relapses and remissions), spleno- and hepatomegaly and generalized lymphadenopathy, bone marrow involvement, and lymphocytic or reticulocytic proliferation. HB could be induced by inoculation of baboons with blood from leukemia patients. The blood plasma of baboons with HB contained viral particles identified as oncornavirus C. Inoculation of four monkeys (*Macaca arctoides*) with a plasma precipitate containing virus particles caused HB in all four. A virus identified as baboon herpesvirus (BHV) was isolated from the bone marrow and spleen cells of baboons with HB. The DNA from BHV showed approx 40%-60% homology with the DNA from Epstein-Barr virus. (55 refs.)

**78-1864 Adenoviruses--Model Systems of Virus Replication, Human Cell Molecular Biology, and Neoplastic Transformation.** (Eng) Green, M. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, 3681 Park Ave., St. Louis, MO, 63110). *Perspect Biol Med* 21(3): 373-397; 1978.

The molecular biology of adenoviruses, oncogenic DNA viruses, is reviewed. Over 80 distinct adenoviruses, including 31 human serotypes, have been isolated from various animal species. Study of these viruses yields information useful to the understanding of virus replication, human cell molecular biology, and neoplastic transformation. Particular attention is focused on the replication of adenovirus 2 (Ad2), the synthesis and mapping of early mRNA species in Ad2-infected and -transformed cells, and adenovirus early proteins. Studies with Ad12 (representative of Group A adenoviruses) and Ad2 (representative of Group C adenoviruses) provided strong evidence that these viruses are not involved in the etiology of human gastrointestinal and lung cancers. Since these viruses have a great deal of genetic similarity to other members of their respective groups, the data also indicate that neither Group A nor Group C adenoviruses are involved in these human cancers. (38 refs)



## CHEMICAL CARCINOGENESIS

- 78-1865 **The Effects of Some Aluminium and Zirconium Compounds on Guinea-Pig Peritoneal Macrophages and Skin Fibroblasts in Culture.** (Eng) Badenoch-Jones, P. (Dept. Pathology, Royal Coll. Surgeons England, Lincoln's Inn Fields, London WC2A 3PN, England); Turk, J. L.; Parker, D. *J Pathol* 124(1): 51-62; 1978.

The effects of aluminum hydroxide [Al(OH)<sub>3</sub>], zirconium hydroxide [Zr(OH)<sub>4</sub>], aluminum chlorhydrate (ACH), and zirconium aluminum glycine complex (ZAGS) on guinea pig peritoneal macrophages and skin fibroblasts in culture were investigated. Incubation of macrophages in medium containing 25% fetal bovine serum with Al(OH)<sub>3</sub> resulted in a rapid release of lactate dehydrogenase (LDH) in a time- and dose-dependent manner. Al(OH)<sub>3</sub> gel, ACH, and ZAGS (1 mg/ml) were cytotoxic, but 8- $\mu$ m particles of Al(OH)<sub>3</sub> and Zr(OH)<sub>4</sub> gel were inactive. With cultured fibroblasts, LDH release was slower and Al(OH)<sub>3</sub>, ACH, and ZAGS gels were damaging but Zr(OH)<sub>4</sub> gel was inactive. Microscopy of the macrophages revealed vacuoles not seen in control cells, and microscopy of the fibroblasts suggested that the gels were phagocytized and the phagosome membrane was dissolved. Macrophages were then cultured with either a nontoxic dose (25  $\mu$ g/ml) or a marginally toxic dose (100  $\mu$ g/ml) of the Al(OH)<sub>3</sub>, ACH, or ZAGS gels for up to 60 hr; however, no increased selective release of lysosomal enzymes could be demonstrated. Al(OH)<sub>3</sub>, ACH, and ZAGS were hemolytic, but Zr(OH)<sub>4</sub> was not. Thus, a correlation exists between the hemolytic properties of these compounds, their toxic effects on macrophages and fibroblasts, and their ability to form granulomas after id injection in guinea pigs (as found in previous studies). (13 refs)

- 78-1866 **Destructive Effect of Methyl Mercury Chloride on Human Mitoses in Living Cells In Vitro.** (Eng) Rozynekowa, D. (Lab. Human Genetics, Dept. Clinical Pathology, Medical Sch. Lublin, 20-950 Lublin, Poland); Raczkiewicz, B. *Mutat Res* 56(2): 185-191; 1977.

Human peripheral WBC were exposed to 0.2-40.0  $\mu$ g/ml methyl mercury chloride (MMC), and cell viability, phytohemagglutinin (PHA)-induced blastogenesis, and c-mitotic activity (arrested metaphases) were determined. The proportion of c mitoses was significantly increased at a concentration of 20  $\mu$ g/ml MMC; with a concentration of 40  $\mu$ g/ml, no mitoses were observed after 2 hr. Both blast cell viability and the blastic index decreased with decrease in the mitotic index, but the percentage of mitotic damage increased. The effects of MMC on all three processes of cell proliferation were dose-

dependent. The chromosomes of each cell became clumped into a dense clump, and they frequently formed a ring configuration, with centromeres being directed toward the center. The ring configuration appeared to be influenced by c-mitotic arrest. A comparison of the c-mitotic efficiency of MMC and colcemid indicated that the former was approximately 100 times weaker than the latter. (7 refs)

- 78-1867 **Lung-Cancer Mortality of Workers Manufacturing Chrome Pigments (Letter to Editor).** (Eng) Davies, J. M. (Div. Epidemiology, Inst. Cancer Res., Surrey SM2 5PX, England). *Lancet* 1(8060): 384; 1978.

In 1975, a lung cancer mortality study was made in three English factories manufacturing chromate pigments. Factories A and B produced lead and, until 1964 and 1967 respectively, zinc chromate pigments, and all workers studied had been exposed to both. Factory C produced lead chromate pigments only. The study group comprised (A) 396 men starting work from 1932 to 1967, (B) 136 starting work from 1948 to 1967, and (C) 114 starting work from 1946 to 1967. Workers starting work after 1967 were excluded because of inadequate follow-up time. Workers were classified by start date and length of service and by level of exposure. At factory A, lung cancer mortality was raised significantly for low and medium-exposure workers who started employment in 1932-1954, but there were no excess deaths among workers with low exposure or < 1 yr of service. There was no excess mortality among men entering employment after 1954, when working conditions were improved. The results were similar for factory B. There was no excess mortality at factory C. Further analysis at factories A and B showed that the excess of deaths for medium-exposure workers was similar to that for high-exposure workers. Exposure for as little as 1 yr was associated with raised mortality (observed/expected death rate = 9/2.97,  $p < 0.01$ ). Induction times were short, with a ratio of observed/expected deaths being fairly constant (1.0) during 5-24 yr after first exposure. The absence of excess cancer mortality at factory C suggests that the hazard at factories A and B arose from the zinc chromate pigments, in agreement with other reports. (7 refs)

- 78-1868 **A Comparison of the Effect of Metal Carcinogens Chromium, Cadmium and Nickel on the Interferon System (Letter to Editor).** (Eng) Pribyl, D. (D



ogy, Univ. San Francisco, San Francisco, CA, 94117);  
gan, L. *Acta Virol (Praha)* 21(6): 507; 1977.

effects of chromium, cadmium, and nickel on the inter-  
feron system were investigated in Newcastle disease virus-  
infected murine fibroblasts (L-929). Although Cd-treated  
cells produced approx twofold lower interferon titers  
compared with controls, the only significant reduction (five-  
fold) occurred in Ni-treated cells. The reduction is probably  
caused by a block in interferon synthesis, rather than a defec-  
t release of cellular interferon. (4 refs)

1869 **Intramuscular Injections of Iron Compounds  
and Oncogenesis in Man.** (Eng) Weinbren, K.  
Dept. Histopathology, Royal Postgraduate Medical Sch.,  
London W12 0HS, England); Salm, R.; Greenberg, G. *Br J J* 1(611): 683-685; 1978.

case reports and clinical material from 7/8 published  
reports of sarcomas developing at the site of im injections of  
iron compounds were evaluated. In only two patients were  
tumors actually believed to have been malignant. The first  
was a 35-yr-old woman who developed a rhabdomyosarcoma  
of the right buttock 13 yr after receiving iron dextran injec-  
tions. The second was a 35-yr-old woman who developed a  
sarcoma of the left buttock 14 yr after four iron dextran  
injections. Tumors resulting from iron injection in animals  
showed a fairly uniform histological appearance and an abun-  
dant number of iron-containing macrophages. Neither the two tu-  
mors mentioned nor the other five examined had a uniform  
histology or iron-containing macrophages. It is suggested  
that in view of the large number of patients who have received  
iron, this treatment carries little risk of tumor develop-  
ment. (28 refs)

1870 **Tumorigenic Effect of an Organomanganese  
Compound on F344 Rats and Swiss Albino  
Mice: Brief Communication.** (Eng) Furst, A. (Inst. Chemical  
Biology, Univ. San Francisco, San Francisco, CA, 94117). *J  
Nat Cancer Inst* 60(5): 1171-1173; 1978.

The carcinogenic effect of pure manganese (Mn) and man-  
ganese dioxide (MDO) was evaluated in F344 rats and Swiss  
albino mice and that of manganese acetylacetonate (MAA)  
was evaluated in the rats. The test materials were adminis-  
tered as fine-powder suspensions in triolein (0.2 ml im or  
0.1 ml by gavage). Groups of rats received the following treat-  
ments: 10 mg Mn/mo im x9; 10 mg MDO/mo im x9; 50 mg  
MAA/mo im x6; or 10 mg Mn 2x/mo po, for a total of 24  
treatments. Groups of mice received 10 mg/mo im x1, or 3  
5 mg MDO/mo im x5. With pure Mn and MDO, there  
was no difference in tumor incidence between treated and  
control (triglyceride-treated) rats and mice. In contrast,  
MAA produced a statistically significant number of fibrosar-

comas at the injection sites in 19/50 rats. Control rats had  
an incidence of 2/50, Mn-treated rats an incidence of 3/50.  
Apparently, the results from one Mn compound cannot be  
extrapolated to all compounds of that element. (12 refs)

78-1871 **Induction of Renal Carcinomas by Intrarenal  
Injection of Nickel Subsulfide in Rats (Meeting  
Abstract).** (Eng) Sunderman, F. W. (Univ. Connecticut Sch.  
Medicine, Farmington, CT, 06032); Maenza, R. M.; Hopfer,  
S. M.; Mitchell, J. M.; Allpass, P. R.; Damjanov, I. *Proc Am  
Assoc Cancer Res* 19: 127; 1978. (1 ref)

78-1872 **Induction of Testicular Sarcomas in Fischer  
Rats by Intratesticular Injection of Nickel Sub-  
sulfide.** (Eng) Damjanov, I. (Dept. Pathology, Hahnemann  
Medical Coll., Philadelphia, PA 19102); Sunderman, F. W.;  
Mitchell, J. M.; Allpass, P. R. *Cancer Res* 38(2): 268-276;  
1978.

Nickel subsulfide ( $\text{Ni}_3\text{S}_2$ ) was injected into the testis of adult  
Fischer rats to study its acute and chronic effects on testicular  
cells. Rats receiving 0.6 - 10 mg of  $\text{Ni}_3\text{S}_2$  developed an im-  
mediate inflammatory response at the injection site, followed  
by a delayed, slowly evolving coagulation necrosis of seminif-  
erous tubules and interstitial cells. The extent of testi-  
cular necrosis was dose dependent but doses of 5 or 10  
mg  $\text{Ni}_3\text{S}_2$  invariably led to subtotal destruction of the  
testis. No damage was seen in the other testis, and no  
systemic effects were noted. Malignant testicular neo-  
plasms developed in 16/19 rats within 20 mo after  
injection of 10 mg  $\text{Ni}_3\text{S}_2$ . These neoplasms were  
classified by light and electron microscopy as fibro-  
sarcomas, malignant fibrous histiocytomas, and rhab-  
domyosarcomas. None of the testicular neoplasms were  
derived from germ cells or genital cord cells. The occurrence  
of rhabdomyosarcomas in the testis, an organ normally de-  
void of striated muscle, suggests that  $\text{Ni}_3\text{S}_2$  induced malignant  
transformation of undifferentiated, pluripotential mesenchy-  
mal cells. (27 refs.)

78-1873 **Chromosome Analyses of Children after Ecolog-  
ical Lead Exposure.** (Eng) Bauchinger, M. (In-  
stitut für Biologie, Gesellschaft für Strahlen- und Umweltfor-  
schung mbH., Neuherberg, W. Germany); Dresch, J.; Schmid,  
E.; Englert, N.; Krause, C. *Mutat Res* 56(1): 75-80; 1977.

Chromosome analysis was performed in a group of 20 chil-  
dren living in a town with a lead smelter who fulfilled at least  
one of the following three criteria indicative of significant  
lead exposure: blood lead level  $\geq 30 \mu\text{g}/100 \text{ ml}$ ,  $\delta$ -  
aminolevulinic acid dehydratase activity  $\leq 25.0 \text{ units/liter}$  of  
blood, or free RBC porphyrin content  $\geq 120.0 \mu\text{g}/100 \text{ ml}$



RBC's. Ten healthy children from areas not exposed to industrial emissions were included as controls. Two hundred cells from each child were scored after 48 hr in culture. Despite the increased lead exposure levels, there was no evidence of a higher number of cells with structural chromosome aberrations or of an increased aberration yield in the exposed children compared with controls. This study confirms previous findings that exposure to environmental lead does not increase chromosome aberration yield. (16 refs)

- 78-1874 Ultrastructural Observations on Epithelioid Cell Granulomas Induced by Zirconium in the Guinea-Pig.** (Eng) Turk, J. L. (Dept. Pathology, Royal Coll. Surgeons England, Lincoln's Inn Fields, London WC2A 3PN, England); Badenoch-Jones, P.; Parker, D. *J Pathol* 124(1): 45-49; 1978.

The ultrastructure of granulomas induced in Hartley strain guinea pigs by sodium zirconium lactate (NaZrL) was investigated. The pigs were immunized in the footpads with 0.1 ml of an emulsion containing 2 mg/ml NaZrL in Freund's complete adjuvant; 0.1 ml was also injected into the nape of the neck. Starting on day 14, they were skin tested by id injection of 25 µg of the salt; this was repeated weekly for five injections. At 7 wk after immunization, 9/10 animals had developed nodular granulomas consisting of monocytes, macrophages, epithelioid cells, multinucleated giant cells, and fibroblasts. The granulomas did not show the organized appearance seen in chronic inflammatory lesions of the tuberculoid type. The epithelioid cells ranged from those containing a modest amount of endoplasmic reticulum (ER) to cells with a larger amount of rough ER, a fimbriated cell membrane with pseudopodia, and a nuclear appearance typical of the more mature epithelioid cell. Multinucleated giant cells were noted at the periphery of the lesion. It appears that the epithelioid and other cells of the mononuclear phagocyte series share a common origin. Although the epithelioid and multinucleated giant cells were similar to those described in Zr granulomas in man, they were not identical to them. (5 refs)

- 78-1875 Tests on Induction of Chromosome Aberrations in Mouse Germ Cells with Sodium Bisulfite.** (Eng) Generoso, W. M. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Huff, S. W.; Cain, K. T. *Mutat Res* 56(3): 363-365; 1978.

The ability of sodium bisulfite to induce chromosomal aberrations in male and female (101 x C3H)F<sub>1</sub> mice was investigated. Males were given multiple ip injections of either 300 or 400 mg/kg/day and females were treated once with 550 mg/kg. Sodium bisulfite did not induce a detectable increase in dominant-lethal mutations in either male or female germ cells, and there were no heritable translocations in male germ cells. (9 refs)

- 78-1876 Theoretical Mechanisms for Synthesis of Carcinogen-induced Embryonic Proteins. I. Alpha-Fetoprotein Induction by Ethionine.** (Eng) Forrester, P. (Div. Medical Biochemistry, Faculty Medicine, Univ. Calgary, Calgary, Alberta, Canada); Hancock, R. L. *Med Hypotheses* 4(1): 31-36; 1978.

The ability of ethionine to induce alpha-fetoprotein was investigated, and a theory concerning the mechanism of this induction was developed. Sprague-Dawley rats were fed a diet containing 1% DL-ethionine followed, in some cases, by one containing 1% DL-methionine. Rat serum alpha-fetoprotein was measured by radioimmunoassay. There was a significant increase in the serum alpha-fetoprotein levels (108 nanograms/ml vs 45.4 in control) after only 72 hr on the 1% DL-ethionine diet. However, these high levels could be reversed by substituting the 1% DL-methionine diet. It is hypothesized that the repressor protein for the alpha-fetoprotein gene (which may be ligandin) must be modified (methylated) before it is functional; if this does not occur, alpha-fetoprotein will not be produced. This theory can explain a variety of states of the liver cell in which alpha-fetoprotein is expressed, ie, fetal, ethionine-treated, neoplastic, and tyrosinemic liver cells. Two lines of evidence suggest that alpha-fetoprotein synthesis and carcinogenesis may be closely related: (1) 60%-80% of all hepatoma patients show elevated levels of this protein in their serum; and (2) several hepatocarcinogens result in a renewed synthesis of alpha-fetoprotein within a few days of the beginning of treatment. (25 refs)

- 78-1877 Rat Liver Microsome Mediated N-Demethylation and Mutagenicity of Azoxymethane (AOM) In Vitro (Meeting Abstract).** (Eng) Campbell, R. L. (Dept. Surgery, Wayne State Univ. Sch. Medicine, Detroit, MI, 48201); Suppnick, J. D.; Hettrick, J. M.; Nigro, M. D. *Proc Am Assoc Cancer Res* 19: 58; 1978. (no refs)

- 78-1878 Mutagenic Effect of Dichloromethane on *Salmonella typhimurium*.** (Eng) Jongen, W. M. (Dept. Toxicology, Agricultural Univ., De Dreijen 12, Wageningen, Netherlands); Alink, G. M.; Koeman, J. H. *Mutat Res* 56(3): 245-248; 1978.

The mutagenicity of dichloromethane (DCM) was tested at concentrations ranging from 5.7 to 57.0 x 10<sup>3</sup> ppm in *Salmonella typhimurium* strains TA98 and TA100. The mutation rate increased with the DCM dose in both strains. Addition of a liver homogenate from phenobarbital-induced rats slightly increased the number of mutations, but it was not essential. It is suggested that the homogenate converts DCM to more active metabolites. (8 refs)



879 **Carcinogen Chemistry. 2. Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of the Independent Carbocationic Nature of Iminium Ions and Its Influence on the Aminoalkylating Ability of Related Chemically Active Compounds.** (Eng) Olah, G. A. (Dept. Chemistry, Case Western Reserve Univ., Cleveland, OH, 44106); Donovan, J. *J Org Chem* 43(5): 860-865; 1978.

13C nuclear magnetic resonance spectroscopic investigations of aliphatic and aromatic iminium ions were performed to determine the extent of the contribution of their iminium ion character. CNDO/2 charge-density calculations of simple aliphatic iminium ions were also performed and related to the 1H and 13C nuclear magnetic resonance chemical shifts. N- and C-methyl substituents were found to increase the charge density of the  $\pi$  bond, resulting in shielding and deshielding effects, respectively. Furthermore, the iminium structures predominated over the aminocarbenium ions when the iminium ions were compared with carbocation ions and protonated ketones. Iminium ions therefore should be able to act as electrophilic aminoalkylating agents with high involvement of their aminocarbenium ion character. (8 refs)

880 **The Effect of the Inhalation of Chlorinated Alkanes on In Vitro Glucuronidation and Dehydrochlorination Reactions in Rat Tissues.** (Eng) Capel, I. D. (Dept., Marie Curie Memorial Foundation, The Chart, Surrey, RH8 0TZ, England); Williams, D. C. *IARC Sci [Cancer]* 6(1): 43; 1978.

Inhalation of methyl chloride, methylene chloride, chloroform, and carbon tetrachloride did not affect uridine diphosphate-glucuronic acid (UDPGA) transferase in male Sprague-Dawley rat liver, kidney, or lung but it did increase microsomal  $\beta$ -glucuronidase levels in the liver and lung. However, total  $\beta$ -glucuronidase activity was decreased in liver, kidney, and lung. (6 refs)

881 **Interaction of Activated Carcinogenic Intermediates of Ethylene Dihalides with Protein-DNA in Mice and Rats Tissues In Vitro (Meeting Abstract).** (Eng) Banerjee, S. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016); Van Duuren, B. L. *Am Assoc Cancer Res* 19: 67; 1978. (no refs)

882 **Hepatic Lesions in Five Subjects Exposed to Vinyl Chloride Including Three Cases of Liver Angiosarcomas.** (Fre) Puech, A. M. (Laboratoire de medecine legale, medecine du travail, toxicologie, La Merci, 38700 Grenoble, France); Fournet, A.; Laulhere, L.; Faure, J.;

Cau, G.; Mallion, J. M. *Arch Mal Prof* 38(9): 787-795; 1977.

Five men who were occupationally exposed to vinyl chloride for 10-26 yr developed lesions of the liver (3 angiosarcomas, 1 adenocarcinoma plus cirrhosis, 1 portal sclerosis). The patients ranged in age from 38 to 63 yr, and they had been employed in various aspects of polymer production (solution polymerization, polymerization, filtration, dying, etc). Work conditions were conducive to intoxication, since the men ate at their place of work and the factories were poorly ventilated. The three angiosarcoma patients died within 4 mo of diagnosis despite hepatectomy and/or chemotherapy. The patient with portal vein sclerosis was not treated but was followed regularly without evidence of change in his symptoms. The last patient died of pulmonary metastases from hepatic adenocarcinoma 1 yr and 4 mo after liver biopsy revealed widespread cirrhosis. (8 refs.)

78-1883 **Mutagenicity of Trichloroethylene (TCE) in Yeast (Meeting Abstract).** (Eng) Bronzetti, G. (Lab. Environmental Mutagenicity, NIEHS, Research Triangle Park, NC, 27709); Zeiger, E.; Frezza, D. *Environ Health Perspect* 20: 237; 1977. (no refs)

78-1884 **Acute Hepatotoxicity of Ethylene, Vinyl Fluoride, Vinyl Chloride, and Vinyl Bromide after Aroclor 1254 Pretreatment.** (Eng) Conolly, R. B. (Dept. Physiology, Harvard Sch. Public Health, Boston, MA, 02115); Jaeger, R. J.; Szabo, S. *Exp Mol Pathol* 28(1): 25-33; 1978.

The hepatotoxicity of ethane, vinyl ethylene, fluoride monomer (VFM), vinyl bromide monomer (VBM), and vinyl chloride monomer (VCM) was determined in male Holtzman rats pretreated with Aroclor 1254. All compounds except ethane caused degeneration and necrosis of the liver. Ethylene, VFM, and VBM should be evaluated for chronic effects in view of their similarity of acute action to VCM, a known carcinogen. (20 refs)

78-1885 **Metabolism of Trichloroethylene by the Isolated Perfused Lung.** (Eng) Dalbey, W. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Bingham, E. *Toxicol Appl Pharmacol* 43(2): 267-277; 1978.

A method for the perfusion of isolated rat and guinea pig lung was developed and used to measure the metabolism of trichloroethylene (TRI). The main features of the perfusion technique included constant-pressure recirculating perfusion with heparinized, autologous, whole blood; cyclic subatmospheric pressure within a temperature-controlled ventilation chamber; and ventilating gas consisting of air containing ap-



prox 5% CO<sub>2</sub>. The perfusions lasted up to 3 hr. Lungs were ventilated with 30-45 ppm TRI beginning 20 min after the start of perfusion; additional concentrations ranging from 24-129 ppm were given for guinea pig perfusions. Trichloroethanol (TCE) was noted in the perfusing blood within 15 min of initial exposure. The amount of TCE in the blood increased linearly with time; the rate of TCE appearance was much higher in the guinea pig preparations. Chloral hydrate and trichloroethanol glucuronide were not observed. Pretreatment of the rats with phenobarbital (75 mg/kg for 4 days) significantly increased TCE formation. Addition of ethanol to rat blood preparations did not affect TCE formation. The stability of the TCE appearance and of the physiological and biochemical parameters indicate that this perfusion system can serve as a useful model for investigations of pulmonary metabolism. (17 refs)

- 78-1886 Sensitive Gas Chromatographic Methods for the Determination of Vinyl Epoxide Synthetase Activity Using Trichloroethylene as a Model Substrate.** (Eng) Malvoisin, E. (Laboratoire de Biotoxicologie, Univ. Louvain, B-1200 Brussels, Belgium); Rollmann, B.; Lhoest, G.; Roberfroid, M.; Mercier, M. *J Chromatogr* 150(2): 345-354; 1978.

To investigate the role of the microsomal enzymatic system in the carcinogenesis and mutagenesis of several chlorinated olefins, an assay for the determination of vinyl epoxide synthetase activity was developed. The method uses trichloroethylene (TCE) as a substrate and measures enzyme activity by determining the concentration of chloral hydrate, the final product of TCE following its reaction with hepatic epoxide synthetase. (29 refs)

- 78-1887 Induction of Lung Tumors in Strain A Mice by Substituted Organo Chlorides and Bromides (Meeting Abstract).** (Eng) Theiss, J. C. (Dept. Community Medicine, Univ. California San Diego, La Jolla, CA, 92093); Shimkin, M. B.; Poirier, L. A. *Proc Am Assoc Cancer Res* 19: 205; 1978. (no refs)

- 78-1888 Human Sister Chromatid Exchange Caused by Methylazoxymethanol Acetate.** (Eng) Evans, L. A. (Dept. Natural Sciences, Medgar Evers Coll., City Univ. New York, Brooklyn, NY, 11225); Kevin, M. J.; Jenkins, E. C. *Mutat Res* 56(1): 51-57; 1977.

The incidence of sister chromatid exchange (SCE) was determined in human WBC cultures treated with methylazoxymethanol acetate (MAM AC). Two concentrations of MAM AC were tested in cultures derived from nine normal men. The concentrations varied from individual to individual, since

they were determined using individual dose-response curves. These curves showed <sup>3</sup>H-thymidine incorporation phytohemagglutinin-stimulated short-term lymphocyte cultures vs MAM AC concentration. Compared with control cultures, the lower concentration (1-20 µg/ml), which was less than the TD<sub>50</sub>, caused a higher incidence of SCE in number of SCE per metaphase in 8/9 individuals. The higher concentration (5-25 µg/ml) not only caused a significant increase in the frequency of SCE compared with control cultures, but it was also toxic, since a significant number of cultures did not have sufficient metaphase spreads for SCE to be evaluated. The cumulative mean value for all control cultures was 5.32 exchanges per cell; that for cultures treated with the higher MAM AC concentration was 10.73. The increase in SCE may be the result of DNA alkylation. (28 refs)

- 78-1889 Acetaldehyde, Not Ethanol, Induces Sister Chromatid Exchanges in Chinese Hamster Cells In Vitro.** (Eng) Obe, G. (Institut für Genetik, Freie Universität Berlin, Arnimallee 5-7, D-1000 Berlin 33, W. Germany); Ristow, H. *Mutat Res* 56(2): 211-213; 1977.

The mutagenicity of methanol, ethanol, propanol, butanol and acetaldehyde was studied in Chinese hamster ovary cells. None of the alcohols were mutagenic, whereas 0.0005% and 0.001% volume/volume concentrations of acetaldehyde induced significant numbers of sister chromatid exchanges. Higher doses (0.003% and 0.004%) of the aldehyde killed the cells. Since acetaldehyde is a metabolite of ethanol in mammals, it may be responsible for the elevation of chromosomal aberrations in alcoholics. (11 refs)

- 78-1890 The Effect of Chronic Ethanol Intake upon Growth and Spread of Some Murine Tumors.** (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 OTL, England); Williams, D. C. *IARC Med Sci [Cancer]* 6(2): 56; 1978.

The effect of ethanol treatment (10% volume/volume solution) on the growth and spread of Lewis lung tumors, Ehrlich ascites tumors, and B16 melanomas in C57/BLL and TO mice was investigated. The mice were given the ethanol 2 wk prior to and after tumor inoculation, or only for 2 wk after inoculation. Chronic ethanol intake did not enhance the growth or spread of the murine tumors. In addition, it decreased both the size of the lung tumors and the number of pulmonary metastases in C57/BLL mice. (5 refs)

- 78-1891 Sister Chromatid Exchanges and Growth Inhibition Induced by the Flame Retardant Tri(2,4,6-tribromopropyl) Phosphate in Chinese Hamster Cells: B**



**Communication.** (Eng) Furukawa, M. (Dept. Experimental Biology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Sirianni, S. R.; Tan, J. C.; Huang, C. C. *J Natl Cancer Inst* 60(5): 1179-1181; 1978.

To determine the mutagenic or carcinogenic potential of the retardant tris(2,3-dibromopropyl) phosphate (Tris-BP) in mammalian cells, its effects on cell growth, chromosomes, sister chromatid exchanges (SCE) were assessed in Chinese hamster V79 cells in vitro and in V79 cells cultured in tissue chambers (DC:  $10^5$  cells) implanted into mice. Adrenal studies were made with two human lymphoid cell lines and mouse bone marrow cells. Tris-BP (0-100  $\mu\text{g}/\text{ml}$ ) caused a dose- and time-dependent reduction of cell growth, measured by colony-forming activities. There was a significant ( $p < 0.001$ ) dose-dependent increase in SCE in V79 cells in cultures treated with Tris-BP (0-50  $\mu\text{g}/\text{ml}$ ) or in DC mice inoculated ip with the chemical (125, 250, 500, or 1000  $\mu\text{g}/\text{g}$ ). In contrast, chromosome aberrations were not increased significantly in V79 cells in DC from hosts that had received doses as high as 1,000  $\mu\text{g}/\text{g}$ , in V79 cells in culture, in the two lymphoid cell lines in culture, or in the mouse bone marrow cells in vivo. (16 refs)

**1892 The Flame Retardant Tris(2,3-dibromopropyl)phosphate: Alteration of Human Chromosomal DNA.** (Eng) Gutter, B. (Dept. Microbiology, New York Medical Coll., Valhalla, NY, 10595); Rosenkranz, H. *Mutat Res* 56(1): 89-90; 1977.

Human KB cells exposed to tris(2,3-dibromopropyl)phosphate (2  $\mu\text{l}/\text{ml}$  of growth medium devoid of serum) for 4.5 hr had a reproducible decrease in the size of their DNA, as revealed by sedimentation. Following incubation without this compound, treated cell DNA sedimented in the same region as the DNA from untreated cells. The evidence of DNA repair indicates that the decreased size of the DNA from treated cells did not reflect nonspecific toxicity. (6 refs)

**1893 Organ Differences in DNA Repair in Cultured Fetal Rat Cells Exposed to Methyl Methanesulphonate (MMS) (Meeting Abstract).** (Eng) Chen, B. P. (NCI, Bethesda, MD, 20014); Berman, J. J.; Rice, J. M. *Proc Am Assoc Cancer Res* 19: 122; 1978. (no refs)

**1894 The Induction In Vivo of Sister Chromatid Exchanges in the Bone Marrow of the Chinese Hamster. I. The Sensitivity of the System (Methyl Methanesulphonate).** (Eng) Marquardt, H. (Forstbotanisches Institut, Universität Freiburg, Freiburg im Breisgau, W. Germany); Bayer, U. *Mutat Res* 56(2): 169-176; 1977.

The mutagenicity of methyl methanesulphonate (MMS) was investigated in vivo in Chinese hamsters. The animals were treated at time 0 with 80 mg/kg fluorodeoxyuridine (FUDR) ip; at 2 hr with 40 mg/kg bromodeoxyuridine (BUdR), 0.2 mg/kg FUDR, and various doses of MMS ip; between 3-8 hr with hourly injections of BUdR and FUDR; and at 24 hr with 10 mg/kg colchicine ip; they were killed at 26 hr. The doses of MMS tested were 1, 5, 10, 25, 50, 75, and 100 mg/kg. There was a relationship between sister chromatid exchanges and MMS dose up to 10 mg/kg. Even a 1-mg/kg dose caused a significant increase in SCE, but at 100 mg/kg, no more intact metaphases could be found. Compared with other cytogenetic methods in vivo, the sister chromatid exchange test proved to be the most sensitive. (23 refs)

**78-1895 Decreased Incidence and Antigenicity of Urethane-induced Lung Adenomas in Nude Mice (Meeting Abstract).** (Eng) Sussdorf, D. H. (Graduate School of Medical Sciences, Cornell Univ. Medical Coll., New York, NY, 10021). *Proc Am Assoc Cancer Res* 19: 50; 1978. (no refs)

**78-1896 Mutagenicity Screening of Five Methyl Carbamate Insecticides and Their Nitroso Derivatives Using Mutants of *Salmonella typhimurium* LT2.** (Eng) Blewett, R. D. (Dept. Health Sciences, East Tennessee State Univ., Johnson City, TN, 37601); Lee, M.; Regan, J. D. *Mutat Res* 56(1): 1-6; 1977.

The mutagenic activity of five methyl carbamate insecticides, carbaryl, baygon, BUX-Ten, landrin, and methomyl, and their nitroso derivatives was tested using histidine auxotrophs (his TA98, his TA100, his TA1535, his TA1537, and his TA1538) of *Salmonella typhimurium* LT2 in the Ames assay. The methyl carbamate insecticides had no significant mutagenic effect with the 50 nM doses used; the NO-carbamates, however, were strongly mutagenic. Strains his TA100 and his TA1535 were strongly reverted by the NO-carbamates, which suggests that this class of compounds may cause base-pair substitutions. It is concluded that the nitroso derivatives of the tested methyl carbamate insecticides are potent mutagens, whereas the parent insecticides are nonmutagenic. (13 refs)

**78-1897 Preventive Role of Vitamin A in Colon Carcinogenesis in Rats.** (Eng) Newberne, P. M. (Animal Pathology Lab., Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Building E18-611, Cambridge, MA 02139); Suphakarn, V. *Cancer* 40(5, Suppl): 2553-2556; 1977.

The effect of vitamin A on colon carcinogenesis in male Sprague-Dawley rats was investigated. In rats exposed



to five weekly doses of 30 mg/kg dimethylhydrazine (DMH) 100% of those deficient in vitamin A developed colon tumors, but only 60% of those supplemented with vitamin A developed tumors. In experiments in which rats were fed 25  $\mu$ g aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) per day for 15 days or AFB<sub>1</sub> was added to the diet at 1 ppm, a significant incidence of colon tumors was noted in rats fed only 0.3  $\mu$ g/g vitamin A. However, rats fed 30  $\mu$ g/g vitamin A had a much-reduced incidence of colon cancer; the incidence of liver cancer was approx the same in both groups. Examinations of the urinary metabolites from these animals indicated that more AFB<sub>1</sub> is excreted in the deficient rats and that there is an additional spot on the thin-layer chromatographs of the depleted AFB<sub>1</sub>-treated rats that is not observed in controls. A comparison of serum and liver vitamin A levels indicated that serum levels are buffered by liver values and that liver concentrations vary with dietary intake. There was a linear decrease in vitamin A from the normal to the depleted colon epithelium to the tumor. Low levels of vitamin A in the diet also decreased liver O-demethylase activity. Both a deficit and excess of vitamin A diminished the capacity of splenic lymphocytes to respond to phytohemagglutinin. Treatment of the DMH animals with 3.0  $\mu$ g/g retinyl acetate and 67  $\mu$ g/g 13-cis-retinoic acid (a vitamin A analog) resulted in a 40% tumor incidence compared to 100% in animals treated with retinyl acetate alone. (11 refs.)

- 78-1898 Tumor Induction with the N-Acetyl Derivative of 4-Hydroxymethylphenylhydrazine, a Metabolite of Agaritine of *Agaricus bisporus*.** (Eng) Toth, B. (Epplēy Inst Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB 68105); Nagel, D.; Patil, K.; Erickson, J.; Antonson, K. *Cancer Res* 38(1): 177-180; 1978.

The tumorigenicity of N'-acetyl-4-(hydroxymethyl)-phenylhydrazine (AMPH), a metabolite of agaritine (B-N[ $\gamma$ -a-L(+)-glutamyl]-4-(hydroxymethylphenylhydrazine), which is found in the commonly eaten cultivated mushroom *Agaricus bisporus*, was examined. AMPH was given as a 0.0625% solution in the drinking water to albino Swiss mice, starting at 6 wk of age and continuing for life. The daily intake of AMPH (based on av daily water consumption) was 6.4 mg for females and 6.6 mg for males. Compared to untreated controls, lung tumor incidence rose from 15% to 34% in treated females and 22% to 48% in treated males. The incidence of blood vessel tumors increased from 8% to 32% in females and from 5% to 30% in males. Histopathologically, the tumors were classified as adenomas and adenocarcinomas of the lungs and angiomias and angiosarcomas of the blood vessels. Since *A. bisporus* contains up to 0.04% agaritine and estimated US consumption was 360,000,000 pounds in 1975, it is suggested that further studies be undertaken on the carcinogenicity of agaritine metabolites. (21 refs.)

- 78-1899 Inhibition of Asbestos-induced Metaplastic Changes and Incorporation of Tritiated Thymidine in Hamster Tracheal Organ Cultures with Addition of the Vitamin A Analog, Retinyl Methyl Ether (Meeting Abstract).** (Eng) Mossman, B. T. (Univ. Vermont Coll. Medicine, Burlington, VT, 05401); Craighead, J. E. *Proc Am Assoc Cancer Res* 19: 93; 1978. (1 ref)

- 78-1900 DNA Damage in Various Tissues of the Mouse Induced by 1,2-Dimethylhydrazine (DMH) (Meeting Abstract).** (Eng) Brambilla, G. (Depts. Pharmacology and Oncology, Univ. Genoa, Genoa, Italy); Cavanna, M.; Sciaba, L.; Parodi, S. *Proc Am Assoc Cancer Res* 15; 1978. (no refs)

- 78-1901 1,2-Dimethylhydrazine-induced Methylation of DNA Bases in Various Rat Organs and the Effect of Pretreatment with Disulfiram (Meeting Abstract).** (Eng) Swenberg, J. (Pathologisches Institut der Universitt Freiburg, Freiburg, W. Germany); Cooper, H.; Buecheler, Kleihues, P. *Proc Am Assoc Cancer Res* 19: 102; 1978. (1 ref)

- 78-1902 Cyclic Nucleotide Concentrations in Dimethylhydrazine Induced Rat Colon Adenocarcinoma.** (Eng) Stevens, R. H. (Radiation Res. Lab. Medical Labs., Univ. Iowa, Iowa City, IA, 52242); Lofgren, D. P.; Osborne, J. W.; Prall, J. P.; Lawson, A. J. *Cancer Res* 38(1): 27-33; 1978.

The intracellular concentrations of cyclic AMP (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP) were measured in colon tumors induced in male Holtzman rats by weekly sc injections of 20 mg/kg 1,2-dimethylhydrazine (DMH). The rats were sacrificed 14 days after the last DMH treatment. The tumor intracellular cAMP concentrations were approx 50% of those measured in normal tissue. Normal-appearing tissue adjacent to the neoplasm had cAMP levels indistinguishable from those in the tumor. cGMP levels in the tumor, however, were almost twice those in normal colon tissue. Levels were also elevated in normal-appearing tissue adjacent to the tumor. A comparison of molar cAMP and cGMP ratios indicated that significant differences existed between normal to tumor tissue and normal to tumor-adjacent tissue. cAMP and cGMP levels were then measured in tumors occurring in different sites in the colon to determine if location had any effect. The results showed relatively consistent cAMP and cGMP levels. Thus, the anomalous tumor cyclic nucleotide concentrations are attributed to the specific population of the lesion and not to the site of development within the colon. (21 refs)

- 78-1903 Correlation Between Karyorrhectic Index and Colon Crypts and Tumor Yield in Dimethylhydrazine**



azine-treated Rats (Meeting Abstract). (Eng) Maskens, A. (Cancer Res. Unit, Clinique Saint-Michel, B-1040 Brussels, Belgium); Dujardin-Loits, R. M. *Proc Am Assoc Cancer Res* 19: 151; 1978. (no refs)

1904 **Inhibitory Effects of Selenium on 1,2-Dimethylhydrazine and Methylazoxymethanol Induced Carcinogenesis. Correlative Studies on Selenium Effects on the Mutagenicity and Sister Chromatid Exchange Rates of Selected Carcinogens.** (Eng) Jacobs, M. M. (Eppley Inst. Res. Cancer, 42nd and Dewey Ave., Omaha, NB 68105). *Cancer* 40(5, Suppl): 2557-2564; 1977.

The effect of selenium (4 ppm in the drinking water) on carcinogenesis in male Sprague-Dawley rats receiving weekly injections of 20 mg/kg 1,2-dimethylhydrazine (DMH) or methylazoxymethanol (MAM) was investigated. Colon tumors were noted in 13/15 animals receiving DMH alone but only 6/15 animals receiving DMH + Se; the difference was significant. There was no significant reduction in MAM tumor induction. Se reduced the total number of colon tumors more than threefold in the DMH-treated animals and nearly twofold in the MAM-treated animals. This reduction was greater in the proximal and distal portions of the colon than in the transverse colon. Coexposure of *Salmonella typhimurium* TA1538 to molar ratios of 10<sup>-5</sup> Se/2-acetylaminofluorene and Se/N-hydroxyacetylaminofluorene (H-OH-AAF) and 300 for Se/N-OH-acetylaminofluorene reduced the mutagenicity to 65%, 68% and 61% of the respective control values (mutagenicity index). With a molar ratio of 100 for Se/N-OH-AAF, the mutagenicity was reduced to 28% of that for the mutagen alone. Preliminary data indicated that MAM was not mutagenic in *S. typhimurium* strains TA1535 and His<sup>+</sup> 5. Exposure of human lymphocyte cultures to 10<sup>-9</sup> to 1.6 x 10<sup>-5</sup> M Se produced sister chromatid exchange (SCE) rates equivalent to the background level (1 SCE's/cell). Coexposure of cultures to 10<sup>-4</sup> M methyl methanesulfonate (32 SCE/cell in culture) and 10<sup>-6</sup> M Se resulted in only 12 SCE's/cell. It is suggested that Se can interrupt some event essential for sister chromatid exchange and thus disrupt carcinogenesis. (19 refs.)

1905 **Changes in Chromosomal Proteins in Colon Cancer. The Complexity and DNA-binding Properties of Tumor-associated Proteins and Evidence for Their Association with the Malignant State in Human Colon Epithelium.** (Eng) Boffa, L. C. (Rockefeller Univ., New York, NY 10021); Allfrey, V. G. *Cancer* 40(5, Suppl): 2584-2591; 1977.

The properties of two classes of nonhistone nuclear proteins

(NHNP) were investigated using colonic tissue from male CFN rats given weekly sc injections of 20 mg/kg 1,2-dimethylhydrazine. The tumor-specific protein class TNP<sub>1</sub> (mol wt 44,000 daltons) showed a high affinity for the DNA, but a second class, TNP<sub>2</sub> (mol wt 62,000), did not bind to DNA. Digestion of tumor chromatin with DNase I under conditions known to digest active genes preferentially resulted in the selective release of TNP<sub>1</sub> class proteins. This suggested that the protein fraction is associated with actively transcribing portions of the genome. Gel electrophoresis of the two classes indicated that both have isoelectric points in the acidic range. TNP<sub>2</sub> shows considerable heterogeneity with major subgroup of proteins of mol wt 61,000, with pI's ranging from 5.6 to 6.5, and another group of proteins of mol wt 63,000, with pI's between 6.2 and 6.8. The TNP<sub>1</sub> class was more acidic, with a major focus over pH 4.85 to 5.25; a single minor component had a pI of 6.5. Examination of human colonic adenocarcinomas indicated that they contain proteins with mol wts similar to TNP<sub>1</sub> and TNP<sub>2</sub>. These proteins are not obvious in the corresponding electrophoretic profiles of NHNP from normal colonic epithelial nuclei or nuclei from polyps of patients with familial polyposis coli at a time when no malignancy is present. (19 refs.)

78-1906 **Mushroom Toxin: N-Methyl-N-formylhydrazine (MFH) Carcinogenesis in Mice (Meeting Abstract).** (Eng) Toth, B. (Eppley Inst., Univ. Nebraska Medical Center, Omaha, NB, 68105); Nagel, D. *Proc Am Assoc Cancer Res* 19: 42; 1978. (no refs)

78-1907 **Tumors Induced in Mice by N-Methyl-N-formylhydrazine of the False Morel *Gyromitra esculenta*.** (Eng) Toth, B. (Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Nagel, D. *J Natl Cancer Inst* 60(1): 201-204; 1978.

The carcinogenic effect of N-methyl-N-formylhydrazine (MFH), which is found in the false morel *Gyromitra esculenta*, was investigated by administration to Swiss albino mice at doses of 0.0156% and 0.0078% in drinking water. All mice fed the higher dose died by 70 wk; all fed the lower dose died by 80 wk; all controls died by 130 wk. In 50 females fed 0.0156% MFH, there were 3 liver tumors, 9 lung tumors, 1 gallbladder tumor and 1 bile duct tumor; the figures for 50 males were 3 liver tumors and 4 lung tumors. In 50 females receiving 0.0078% MFH, 22 had liver tumors, 30 lung tumors, 4 gallbladder tumors and 2 bile duct tumors; the corresponding figures for 50 males were 11, 20, 5, and 5, respectively. In 100 female controls, there were 15 lung tumors; in 100 male controls, there were 2 liver tumors and 22 lung



tumors. The histopathology of the various tumors is presented. Because of the high level of MFH in *Gyromitra esculenta*, humans should not eat this mushroom. (25 refs.)

- 78-1908 Quantitation of Carcinogen-DNA Adducts by Radioimmunoassay (Meeting Abstract).** (Eng) Poirier, M. (NCI, Bethesda, MD, 20014); Weinstein, I. B.; Blobstein, S.; Yuspa, S. H. *Proc Am Assoc Cancer Res* 19: 119; 1978. (no refs)

- 78-1909 Mutagenicity of Hydroxamic Acids for *Salmonella typhimurium*.** (Eng) Wang, C. Y. (Div. Clinical Oncology, Dept. Human Oncology, Univ. Wisconsin Center Health Sciences, Madison, WI, 53706). *Mutat Res* 56(1): 7-12; 1977.

The mutagenicity of p-butoxyphenylacetohydroxamic acid, benzohydroxamic acid, salicylhydroxamic acid, 2-naphthohydroxamic acid, indole-2-carboxyhydroxamic acid, and benzoylaminoacetohydroxamic acid for *Salmonella typhimurium* strains TA98 and TA100 was determined using the Ames assay method. Except for p-butoxyphenylacetohydroxamic acid, all the hydroxamic acids were mutagenic for both strains. The mutagenicity progressed in the following order: 2-naphthohydroxamic acid > benzohydroxamic acid and salicylhydroxamic acid > benzoylaminoacetohydroxamic acid and indole-2-carboxyhydroxamic acid. p-Butoxyphenylacetic acid, ethyl benzoate, ethyl salicylate, ethyl indole-2-carboxylate, 2-naphthoic acid, hippuric acid and hydroxylamine, the starting materials for the synthesis of these hydroxamic acids, were not mutagenic for either TA98 or TA100. These results suggest that although the mutagenicity may require the hydroxamic acid as a whole, the acyl group may determine the mutagenic potency. (23 refs)

- 78-1910 Effects of Chemical Structure of N-Hydroxy-N-fluorenylacylamides on Arylhydroxamic Acid Acyltransferase, Sulfotransferase and Deacylase Activities, and on Mutations in *Salmonella typhimurium* (Meeting Abstract).** (Eng) Allaben, W. T. (Natl. Center Toxicological Res., Jefferson, AR, 72079); Weeks, C. E.; Louie, S. C.; Lazear, E. J.; King, C. M. *Proc Am Assoc Cancer Res* 19: 235; 1978. (no refs)

- 78-1911 Cellular Analysis of Rat Liver Neoplastic Development Using a Variety of Markers Both In**

**Vivo and In Vitro (Meeting Abstract).** (Eng) Williams, M. (Naylor Dana Inst. Disease Prevention, Valhalla, NY 10595); San, R. H.; Hirota, N. *Proc Am Assoc Cancer Res* 19: 47; 1978. (2 refs)

- 78-1912 Chemical Mitogens as Effective Alternatives to Partial Hepatectomy in the New Model for Sequential Analysis of Hepatocarcinogenesis (Meeting Abstract).** (Eng) Cameron, R. (Univ. Toronto, Toronto, Ontario M5G1L5, Canada); Lee, G.; Farber, E. *Proc Am Assoc Cancer Res* 19: 56; 1978. (no refs)

- 78-1913 Use of the Submaxillary Gland Ducts of Rats Treated with Acetaminofluorene to Demonstrate the Protective Effect of Beta-Naphthoflavone (Fre)** Stora, C. (U.E.R. de Medecine, Laboratoire d'Immunologie, chemin de Vallombrose, 06034 NICE Cedex, France). *C R Acad Sci [D] (Paris)* 285(1): 1271-1273; 1977.

The protective effect of  $\beta$ -naphthoflavone against carcinogen acetaminofluorene (AAF) in rats was evaluated by observation of atrophic changes in the submaxillary gland. Male Wistar rats were fed a normal diet containing 0.015%  $\beta$ -naphthoflavone or 0.015% AAF or both agents. In rats given AAF alone, atrophic changes were observed within 60 days and by day 225 atrophy of the gland ducts was total. When the rats of this group were sacrificed on day 225, hepatocellular carcinoma was observed in all animals. Rats given  $\beta$ -naphthoflavone in addition to AAF did not have signs of atrophy in the submaxillary gland throughout the period of experiment, and animals sacrificed at the end of experimental period did not have hepatic tumors. It is suggested that alterations in the submaxillary gland of AAF-tested rats can be used as a relatively simple method of testing protective or anticancer agents. (6 refs.)

- 78-1914 Production of a Dimer of N-Hydroxy-2-Acetylaminofluorene (2AAF) During the Synthesis of N-Hydroxy-2-Acetylaminofluorene (NOH-2AAF) (Meeting Abstract).** (Eng) Andrews, L. S. (NIH, Bethesda, MD, 20014); Pohl, L. R.; Hinson, J. A. *Proc Am Assoc Cancer Res* 19: 147; 1978. (no refs)

- 78-1915 Induction of Microsomal N-Hydroxylation of N-2-Fluorenylacetamide in Rat Liver.** (Eng) Malejka-Giganti, D. (Lab. Cancer Res., Veterans Ad



, Minneapolis, MN, 55417); McIver, R. C.; Glasek, A. L.; Gutmann, H. R. *Biochem Pharmacol* 27(1): 1978.

possibility that N-2-fluorenylacetamide (2-FAA) in its own microsomal N-hydroxylation was investigated. One or multiple ip injections of 2-FAA [0.1 milligram (mmol)/kg] into Sprague Dawley rats increased N-hydroxylation of 2-FAA by hepatic microsomes 12 times without changing the content of microsome hemoprotein (cytochrome P-450 or P<sub>1</sub>-450). The reaction could be inhibited by carbon monoxide treatment, indicating that either cytochrome P-450 or P<sub>1</sub>-450 is the terminal oxidase in microsomal N-hydroxylation. Unlike pretreatment of rats with 0.075 mg/kg 3-methylcholanthrene or 0.3 mmol/kg phenobarbital, 2-FAA did not appear to induce the synthesis of microsome hemoprotein. The activities of NADPH-cytochrome c reductase, NADPH-cytochrome P-450 reductase, and amine oxidase in the microsomes of 2-FAA-treated rats were not altered and thus did not account for the stimulation of N-hydroxylation. It is concluded that 2-FAA induces an unknown electron carrier associated with the hepatic mixed-function oxidase system. (36 refs.)

916 **Reduction in Acetylaminofluorene (AAF) Hepatocarcinogenesis by Selenium** (Meeting Abstract). (Eng) Marshall, M. V. (Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Jacobs, M. M.; Griffin, A. C. *Proc Am Assoc Cancer Res* 19: 75; 1978. (no refs)

917 **A New Radiochemical Assay for Arylamidation and Arylation of DNA by the Carcinogenic Aromatic Amides** (Meeting Abstract). (Eng) Fuchs, R. P. (Groupe de Biophysique, Institut de Biologie Moléculaire et Cellulaire, 15 rue Descartes, 67084 Strasbourg, France); Fuchs, M. C.; Daune, M. P. *Proc Am Assoc Cancer Res* 19: 1978. (1 ref)

918 **The Metabolic Activation of 2-Acetylaminofluorene by Cells in Culture** (Meeting Abstract). (Eng) Raineri, R. (NCI-Frederick Cancer Res. Center, Frederick, MD, 21501); Pooley, J. A.; Pienta, R. J. *Am Assoc Cancer Res* 19: 61; 1978. (no refs)

919 **Covalent Intercalative Binding of N-Acetoxy-2-Acetylaminofluorene and Hydrocarbon Epoxides to DNA** (Meeting Abstract). (Eng) Drinkwater, N. R.

(McArdle Lab., Univ. Wisconsin, Madison, WI, 53706); Miller, E. C.; Miller, J. A. *Proc Am Assoc Cancer Res* 19: 25; 1978. (2 refs)

78-1920 **The PN Antigen is Altered Epoxide Hydrase in AAF Induced Rat Liver Nodule Microsomes** (Meeting Abstract). (Eng) Griffin, M. J. (Oklahoma Medical Res. Foundation, Oklahoma City, OK, 73104); Kizer, D. E.; Levin, W. *Proc Am Assoc Cancer Res* 19: 58; 1978. (no refs)

78-1921 **Alterations in Cyclic AMP-dependent Protein Kinase Activity Profiles in the Liver in Response to Long-Term Acetylaminofluorene Treatment** (Meeting Abstract). (Eng) Russell, D. H. (Univ. Arizona Health Sciences Center, Tucson, AZ, 85724); Fuller, D. J.; Byus, C. V.; Norvell, M. J. *Proc Am Assoc Cancer Res* 19: 124; 1978. (no refs)

78-1922 **Comutagenic Effect of Norharman and Harman with 2-Acetylaminofluorene Derivatives**. (Eng) Umezawa, K. (Dept. Molecular Oncology, Inst. Medical Science, Univ. Tokyo, Minato-ku, Tokyo 108, Japan); Shirai, A.; Matsushima, T.; Sugimura, T. *Proc Natl Acad Sci USA* 75(2): 928-930; 1978.

The effect of norharman and harman on the mutagenicity of 2-acetylaminofluorene (AAF) derivatives was investigated in the *Salmonella* test system. The mutagenicities of AAF, 2-aminofluorene, and N-hydroxy-2-acetylaminofluorene were enhanced by norharman only when rat liver microsomal enzymes were added, whereas the mutagenicity of N-acetoxy-2-acetylaminofluorene was increased in the absence of microsomal enzymes. Harman also increased mutagenesis, but less so than norharman. Addition of norharman did not enhance the mutagenicity of N-hydroxy-2-aminofluorene, 2-nitrofluorene, or benzo(a)pyrene. The findings suggest that norharman and harman might interact with DNA, altering its conformation and increasing its affinity for mutagens. (14 refs)

78-1923 **Lipid Requirement for 2-Acetylaminofluorene (AAF) N- and Ring Hydroxylation by Reconstituted Hamster Liver Microsomal Enzyme System** (Meeting Abstract). (Eng) Hong, Y. S. (Fels Res. Inst., Temple Univ. Medical Sch., Philadelphia, PA, 19140); Lotlikar, P. D. *Proc Am Assoc Cancer Res* 19: 128; 1978. (1 ref)

78-1924 **In Vitro Metabolism and Mutagenic Activation of 2-Acetylaminofluorene (AAF) and N-Hydroxy-AAF (N-OH-AAF) by Cotton Rat Liver Subcellu-**



lar Fractions (Meeting Abstract). (Eng) Schut, H. A. (NCI, NIH, Bethesda, MD, 20014); Thorgeirsson, S. S. *Proc Am Assoc Cancer Res* 19: 47; 1978. (no refs)

**78-1925 Preferential Carcinogen Modification of Specific Hepatic Chromatin Fractions (Meeting Abstract).** (Eng) Schwartz, E. L. (Dept. Pharmacology, Michigan State Univ., E. Lansing, MI, 48824); Goodman, J. I. *Proc Am Assoc Cancer Res* 19: 34; 1978. (no refs)

**78-1926 Nuclear Metabolism of 2-Acetylaminofluorene (AAF) and 2-Aminofluorene (AF) (Meeting Abstract).** (Eng) Stout, D. L. (M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Becker, F. F. *Proc Am Assoc Cancer Res* 19: 92; 1978. (no refs)

**78-1927 2-Acetylaminofluorene Metabolism, Binding to DNA, and Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures (Meeting Abstract).** (Eng) Casciano, D. A. (Natl. Center Toxicological Res., Jefferson, AR, 72079); Beland, F. A.; Oldham, J. W.; Stanley, J. W.; Jackson, C. D. *Proc Am Assoc Cancer Res* 19: 66; 1978. (no refs)

**78-1928 State of Microsomal Oxygenase System after Chronic Administration of 2-Acetylaminofluorene.** (Rus) Koblyakov, V. A. (Cancer Res. Center, Moscow, USSR); Kolyada, A. Yu. *Vopr Med Khim* 24(1): 113-118; 1978.

The effect of 2-acetylaminofluorene (AAF) on the microsomal oxygenase enzyme system (MOES) was studied in random-bred albino rats. The animals were kept on a synthetic diet containing 0.06% AAF. To induce the MOES, rats received ip injections of phenobarbital (75 mg/kg, for 4 days prior to sacrifice) or 20-methylcholanthrene (20 mg/kg, for 2 days prior to sacrifice). At various times after the initiation of chronic exposure to AAF, rats were sacrificed and the content of cytochromes P-450 and P-448 in the liver microsomes was assessed spectrophotometrically. The AAF administration resulted in a significant decrease in P-450 content starting on the seventh week of exposure and an increase in NADPH-cytochrome reductase activity. (16 refs)

**78-1929 Kinetics of Preneoplastic Epithelia of the Intestinal Mucosa Induced in Buffalo Rats by Oral Administration of N,N'-2,7-Fluorenylenebisacetamide.** (Eng) Yamada, S. (Lab. Pathology, Aichi Cancer Center Res. Inst., 81-1159, Kanokoden, Tashiro-cho, Chikusa-ku, Na-

goya 464, Japan); Ito, M.; Nagayo, T.; Okumura, Y. *Carcinogenesis* 18(6): 805-811; 1977.

A diet containing 0.025% N,N'-fluorenylenebisacetamide (2,7-FAA) was administered to 18 Buffalo rats for 3 mo and to 21 rats for 5 mo, regimens that corresponded, respectively, to the nonneoplastic and preneoplastic stages of carcinogenesis of the intestinal mucosa. During these stages, the mitotic index, labeling index, and generation time of the intestinal mucosa epithelia were estimated by autoradiography. The mitotic index and labeling index values were lower in the rats fed 2,7-FAA for 3 mo than in the untreated controls. Decreases in both indices were also observed in the rats fed 2,7-FAA for 5 mo, except for the proximal part of the colon. A 1-hr delay in the epithelial generation time was observed in rats fed 2,7-FAA for 5 mo compared with the controls; this was mainly due to the prolongation of the G1 phase. A 2- or 3-hr delay in the generation time occurred in the epithelia of rats fed 2,7-FAA for 5 mo and this was mainly due to the prolongation of the S phase. (17 refs)

**78-1930 In Vitro and In Vivo Indications of the Carcinogenicity and Toxicity of Food Dyes.** (Eng) Price, P. J. (Microbiological Associates, Torrey Pines Center, La Jolla, CA, 92037); Suk, W. A.; Freeman, A. E.; Lane, W. T.; Peters, R. L.; Vernon, M. L.; Huebner, R. *Int J Cancer* 21(3): 361-367; 1978.

Eight food dyes or commercial color mixtures, Brilliant Blue FCF (Blue No. 1), Indigotine (Blue No. 2), Fast Green FCF (Green No. 3), Erythrosine (Red No. 3), Ponceau SX (Red No. 4), Tartrazine (Yellow No. 5), Sunset Yellow FCF (Yellow No. 6) and G2024 (a mixture of Blue No. 1 and Yellow No. 5) were tested for their ability to transform F1706 hamster rat embryo cells. All eight coloring agents were tested for use in the US. The dye solutions were sterilized by autoclaving before the tests were performed. Malignant transformation was induced by G2024, Blue No. 2, Green No. 3, and Yellow No. 4. Transformation was not induced by Blue No. 1, Red No. 3, Yellow No. 5, and Yellow No. 6. Suckling L-V-Graffi hamsters were inoculated sc and/or ip with 1-1.5 ml of dye in 0.1 ml of saline, and the animals were monitored for tumor induction and death over a 330-day period. None of the nontransforming dyes or Green No. 3 increased tumor incidence significantly. However, Blue No. 2, G2024, Red No. 4 increased tumor incidence (mostly lymphomas) and/or mortality in at least one strain of hamster. Similar in vitro and in vivo tests indicated that these dyes may be carcinogens, further evaluation is necessary to safeguard the public. (18 refs)

**78-1931 Lack of Mutagenic Activity of a Series of Food Dyes for *Salmonella typhimurium*.** (Eng) Ames, B. N.; Ta, A. E. (Mutagenesis and Transformation Screening



Microbiological Associates, Bethesda, MD, 20016);  
ava, J. M.; Parmar, A. S. *Mutat Res* 56(2): 203-206; 1977.

C red dyes No. 2, 3, and 4 (Amaranth, Erythrosine, and  
eaux SX) and FD&C blue dyes Nos. 1 and 2 (Brilliant  
FCF, and Indigotine) were tested for mutagenicity in  
*Salmonella typhimurium* with and without an exogenous  
of mammalian enzymes for metabolic activation.  
e of the dyes were mutagenic in this test, even though  
is evidence that they can transform cultured rat embryo  
blasts. (11 refs)

932 **Morphologic and Biologic Correlation of  
Hyperplastic and Neoplastic Renal Lesions Oc-  
curring in Buffalo and Fischer Strain Rats Ingesting  
(4-Fluorobiphenyl)acetamide.** (Eng) Reuber, M. D.  
Frederick Cancer Res. Center, P.O. Box B, Frederick,  
21501). *Tumori* 63(6): 493-502; 1977.

ed Buffalo and Fischer rats were fed a diet containing  
g N-4-(4'-fluorobiphenyl)acetamide/100 g diet for 36 wk  
ee if there is a biologic and morphologic correlation  
ng the kidney lesions induced. Tissue from areas or  
les of hyperplasia, small carcinomas ( $\leq 5$  mm) and well-  
developed carcinomas ( $> 5$  mm) was removed and trans-  
planted sc in the groin of weanling isologous rats. Areas and  
les of hyperplasia did not survive upon transplantation,  
2/3 small carcinomas in Buffalo rats and 1/1 in Fischer  
survived and grew. Nine of 10 large carcinomas in Buf-  
rats and 9/9 in Fischer rats also survived. The tumors  
ed 6-8 cm in diameter and then killed their hosts; no  
stases were observed. The histology of the transplanted  
ors was the same as that of the primary tumors. These  
ngs support the contention that there is a gradual transi-  
from a state of dependency to one of autonomy in neo-  
a. (21 refs)

933 **Transformation of C3H 10T1/2 CL8 Cells by  
Photoaffinity Label Derivatives of Fluorene  
ing Abstract).** (Eng) Sarraf, A. M. (Dept. Pharmacolo-  
Univ. Alabama, Birmingham, AL, 35294); DiVito, N.;  
te, W. E. *Proc Am Assoc Cancer Res* 19: 75; 1978. (no

934 **Mutagenicity of Hair Dye Components Relative  
to the Carcinogen Benzidine in *Drosophila*  
*melanogaster*.** (Eng) Fahmy, M. J. (Chemical Carcinogenesis  
Pollards Wood Res. Station, Inst. Cancer Res., Nightin-  
Lane, Chalfont St. Giles, Buckinghamshire HP5 4SP,  
England); Fahmy, O. G. *Mutat Res* 56(1): 31-37; 1977.

Comparative assay was undertaken in *Drosophila melano-*

*gaster* to assess the mutagenic efficiency of the hair dye com-  
ponents m-toluenediamine (m-TD) and 4-nitro-o-  
phenylenediamine (4-NOPD) relative to the aromatic amine  
human carcinogen benzidine (Bzd). The compounds were  
given by microinjection into the hemocoel of adult males in  
equimolar dose ranges (5-20 mM), and their mutagenicities  
were measured separately on the various stages of spermatog-  
genesis. Genetic activity was simultaneously assayed with re-  
spect to the overall induction of the X-chromosome recessives  
(lethals and visibles) relative to the specific effects on riboso-  
mal DNA (rDNA), as *bobbed* mutations. All compounds ex-  
erted decisive mutagenicity both on the X-chromosome and  
the RNA genes, although their activities on the different gen-  
ic sites varied between compounds and as a function of cell  
stage, but not in response to changes in dose, within the inves-  
tigated molarity range. The mutagenicities and selectivities  
of the compounds for rDNA gradually decreased in the order  
Bzd > m-TD > 4-NOPD. These results indicate that the  
carcinogenic hazards of hair dyes in animals, possibly includ-  
ing humans, might not be as great as was suspected on the  
basis of the Ames test, but they are not evidence of their  
complete safety. (23 refs)

78-1935 **The Absorption of p-Toluenediamine by the  
Skin of Rats and Dogs.** (Eng) Hruby, R. (Res.  
Center, Inst. Biology, Seibersdorf, Austria). *Food Cosmet  
Toxicol* 15(6): 595-599; 1977.

The cutaneous absorption of the hair dye constituent p-  
toluenediamine (TD), in formulations similar to those used  
in hair-dyeing, was investigated in Sprague-Dawley rats and  
beagle dogs. Five experiments were conducted: (1) cutaneous  
application to rats of formulation 1 or 2 (0.5 g containing 7.5  
mg or 7.5 g TD) for 30 min; (2) sc administration to rats (1  
ml 0.4% aqueous TD soln); (3) po administration to rats (1  
ml 1.6% soln); (4) cutaneous application to dogs of formula-  
tion 3 (50 ml containing 1.4 g TD) for 3 hr; (5) iv administra-  
tion to dogs (0.224 g TD HCl in 27.0 ml water) for 3 hr.  
In experiment 1, about 0.2% TD was absorbed from each  
formulation, and the absorbed substance was excreted mainly  
in the urine. Upon sacrifice 24 hr later, a residue of 5.2%-  
9.3% of the dose was found in the area of the treated skin.  
Experiments 2 and 3 also showed rapid elimination of TD.  
In experiment 4, about 0.13% of the administered dose was  
absorbed, and 0.92% and 0.840% were excreted in the urine  
and feces, respectively, over 4 days. Blood levels reached a  
peak at 6 hr. Peak blood levels were reached within 2 hr in  
experiment 5. Total amounts excreted in the urine and feces  
were 60% and 19% of the infused dose, with the bulk of the  
4-day excretion occurring in the first 24 hr. The results sug-  
gest that a very small amount of TD is absorbed by the skin  
during hair dyeing. (7 refs)

78-1936 **Induction of Sister Chromatid Exchanges in  
Chinese Hamster Cells by the Hair Dye Con-**



stituents 2-Nitro-p-Phenylenediamine and 4-Nitro-o-Phenylenediamine. (Eng) Perry, P. E. (M.R.C. Clinical & Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh EH4 2XU, England); Searle, C. E. *Mutat Res* 56(2): 207-210; 1977.

The effect of the hair dyes 2-nitro-p-phenylenediamine (2-NPPD) and 4-nitro-o-phenylenediamine (4-NOPD) on the frequency of sister chromatid exchanges (SCE) was determined in cultured Chinese hamster cells. In a preliminary experiment, 2-NPPD was tested at 10-100 µg/ml in hot water and 4-NOPD was tested at 25-200 µg/ml in dimethyl sulfoxide soln. All concentrations induced SCE, the highest levels giving 105.7 (2-NPPD) and 96.10 (4-NOPD) SCE/cell. Slightly lower figures were obtained with unpurified compounds. At concentrations of  $10^{-3}$  to  $10^{-2}$  M, both dyes induced SCE in a dose-dependent manner, 2-NPPD being slightly more effective than 4-NOPD. Both dyes were more potent than ethyl methanesulfonate at the same molarities. These findings support the evidence that some hair dyes are mutagenic; as a result, they are suspected of also being carcinogenic. (14 refs)

78-1937 **Carcinogenicity of Diaphene NN.** (Rus) Pylev, L. N. (Lab. Carcinogens, Cancer Res. Center, Moscow, USSR); Kulagina, T. F.; Smetanin, E. E. *Vopr Onkol* 23(12): 75-77; 1977.

The blastomogenic activity of diaphene NN was tested on CC57 albino mice. Animals received diaphene NN sc (40 mg 1x/wk for 20 mo) or po (40 mg 5x/wk for 15 mo and then 3x/wk for 5 mo). The carcinogenic properties of the agent were more pronounced after sc administration: 55% of the animals developed leukemias and 32% of the mice developed sc sarcomas (the first tumors were detected 4.5 mo after initiation of the experiment). After po administration, 34% of the mice developed leukemias and 5% developed liver tumors (the first tumors were detected 4 mo after initiation of the experiment). Although 36% of the controls also developed leukemias, the first tumors were detected after 11-14 mo of observations. (1 ref)

78-1938 **Occupational Styrene Exposure and Chromosomal Aberrations.** (Eng) Meretoja, T. (Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Helsinki, Finland); Vainio, H.; Sorsa, M.; Harkonen, H. *Mutat Res* 56(2): 193-197; 1977.

The chromosomes in the cultured blood lymphocytes from 10 men (aged 20-41 yr) with 0.6-8.5 yr of occupational exposure to styrene were analyzed, and the results were compared with those in 5 controls (aged 30-35 yr) with no styrene exposure. The incidence of cellular aberrations ranged from 11% to 26% in the lymphocytes of exposed subjects; the incidence

was  $\leq 3\%$  in the control group. There was no correlation between urinary mandelic acid concentrations and chromosomal damage. (10 refs)

78-1939 **The Mutagenic Properties of Chemical Carcinogens and the Relationship of this Property to Possible Mechanisms of Neoplastic Induction.** (Eng) Sick, D. J. (Dept. Genetics and Cell Biology, Litton Bionics Inc., Kensington, MD). In: *Carcinogens: Identification and Mechanisms of Action. Proceedings of the Thirty-First Annual Symposium on Fundamental Cancer Research Held at University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, NCI, American Cancer Society. (Austin, Texas).* 6 pp.; (no refs)

78-1940 **Covalent Binding of Weak Chemical Carcinogens Such as Benzene, Estrone, Ethinylestradiol, and Saccharin to DNA of Rat Liver In Vivo (Meeting Abstract).** (Eng) Lutz, W. K. (Inst. Toxicology, Federal Institute for Environmental Health, 8603 Schwerzenbach, Switzerland); Jaggi, C.; Schlatter, C. *Proc Am Assoc Cancer Res* 19: 13; 1978. (no refs)

78-1941 **Evidence of Heterogeneity of Hepatic and Mononuclear Epoxide Hydratase (EH) Activity in Inbred Strains of Mice (Meeting Abstract).** (Eng) Radtke, E. (Microbiological Associates, Bethesda, MD, 20814); Rude, T. H.; Kouri, R. E. *Proc Am Assoc Cancer Res* 19: 1978. (no refs)

78-1942 **Mutagenic Activity of Some Centrally Active Aromatic Amines in *Salmonella typhimurium*.** (Eng) White, T. J. (Biochemistry Dept., 420 Henry Madison, WI, 53706); Goodman, D.; Shulgin, A. T.; Cerni, N.; Lee, R.; Petrakis, N. L. *Mutat Res* 56(2): 199; 1977.

Several centrally active aromatic amines and their precursors, metabolites, and analogs were assayed for mutagenicity in *Salmonella typhimurium*. Weak mutagenic activity was detected with 5 mg 3,4-methylenedioxymphetamine and 2,5-dimethoxyamphetamine, but the other eight compounds were not mutagenic. This finding could result from the absence of the appropriate metabolic activity. (23 refs)

78-1943 **Mutagenicity of Some Congeners of Benzo(a)pyrene in the *Salmonella typhimurium* Assay System.**



g) Lazear, E. J. (Div. Mutagenesis Res., Natl. Center for Microbiological Res., Jefferson, AR, 72079); Louie, S. C. *Cancer Lett* 4(1): 21-25; 1978.

benzidine, 4-aminobiphenyl, 3,3'-dimethylbenzidine, 3,3'-methoxybenzidine, and 3,3'-dichlorobenzidine were tested for mutagenicity using *Salmonella typhimurium* strains TA98 and TA100. Only 4-aminobiphenyl was mutagenic in both tester strains. 3,3'-Dichlorobenzidine was the only compound that was mutagenic without the addition of the S-9 enzyme mix from uninduced mice. When hydrochloride salts of the parent compounds were made to improve their stability, mutagenicity in the tester strains was reduced except for that of 3,3'-dimethylbenzidine. (12 refs)

1944 **Nonmutagenicity of Tetrabromophthalic Anhydride and Tetrabromophthalic Acid in the Ames *Salmonella*/Microsome Mutagenicity Test.** (Eng) Macgregor, J. T. (Western Regional Res. Lab., Agricultural Research Service, U.S. Dept. Agriculture, Berkeley, CA, 94710); Friedman, M. *Mutat Res* 56(1): 81-83; 1977.

The mutagenicity of the flame retardant tetrabromophthalic anhydride (TBPAn) and tetrabromophthalic acid (TBPAC) was evaluated in the *Salmonella typhimurium*/microsome mutagenicity test. TBPAn and TBPAC were tested at levels from 10 to 10,000  $\mu$ g/plate in strains TA100, TA98, TA1537, and TA1535. Neither TBPAn nor TBPAC exhibited mutagenic activity in any of the four tester strains, either with or without the in vitro microsome-metabolizing system. In contrast, the flameproofing agent tris-(2,3-dibromopropyl)phosphate was a highly effective mutagen in strains TA100 and TA1535 in the presence of the in vitro metabolizing system. The mutagenicity of tris-(2,3-dibromopropyl)phosphate may be due to alkylation of sensitive sites in DNA by carbonium ions derived from the cleavage of aliphatic carbon-bromine bonds. The aromatic carbon-bromine bonds present in TBPAn are relatively inert, so that this compound and its corresponding diacid are less likely to act as biological alkylating agents. (9 refs)

1945 **Mutagenicity of the Epoxide-Diol Metabolites of Saprole and Their Analogs in *Salmonella typhimurium*.** (Fre) Dorange, J. L. (Station de Technologie des Produits Vegetaux, INRA, 7, rue Sully, 21034 Dijon Cedex, France); Delaforge, M.; Janiaud, P.; Padieu, P. *C R Soc Biol Paris* 171(5): 1041-1048; 1977.

The mutagenicity of saprole and its metabolites and analogs saprole, methylene dioxybenzene, 2',3'-epoxysaprole, 1'-hydroxy-2',3'-epoxysaprole, 2',3'-epoxyeugenol, 2',3'-epoxyeugenol methylether, 2',3'-epoxyestragol, 2',3'-epoxyallylbenzene, 2',3'-epoxypropanol, and 2',3'-dihydrodihydroxysaprole was studied in *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA1538, and

TA98. At 200 nanomoles (nmol) per petri dish, none of the substances tested were mutagenic with respect to TA1537, TA1538 and TA98. Only the epoxy metabolites of saprole were mutagenic for TA1535 and TA100. The minimum quantities (nmol/petri dish) causing significant mutation in TA1535 were 6 for 2',3'-epoxysaprole and 2',3'-epoxyestragol; 20 for 1'-hydroxy-2',3'-epoxysaprole, 2',3'-epoxyeugenol methylether, 2',3'-epoxyallylbenzene, and 2',3'-epoxypropanol; and 200 for 2',3'-dihydrodihydroxysaprole. The corresponding values found in TA100 were 2 for 2',3'-epoxysaprole, 2',3'-epoxyeugenol, 2',3'-epoxyestragol; 6 for 1'-hydroxy-2',3'-epoxysaprole, 2',3'-epoxyeugenol methylether, 2',3'-epoxyallylbenzene, and 2'-epoxypropanol and 200 for 2',3'-dihydrodihydroxysaprole. The mutagenicity of the metabolites may be correlated with their electrophilic properties. The results confirm the promutagen character of saprole and its analogs and the role of the epoxides as proximal carcinogens. (14 refs)

78-1946 **The Mutagenicity and DNA-damaging Activity of Cyclic Aliphatic Sulfuric Acid Esters.** (Eng) Braun, R. (Zentralinstitut für Genetik und Kulturpflanzenforschung der Akademie der Wissenschaften der DDR, Corrensstrasse 3, DDR-4325 Gatersleben, E. Germany); Fischer, G. W.; Schoneich, J. *Chem Biol Interact* 19(2): 241-252; 1977.

The mutagenicity and DNA-damaging activity of three cyclic aliphatic sulfuric acid esters were determined by the *Salmonella typhimurium* plate test. The mutagenicity results (reference compounds are included) were 1,3-propane sulfone > 1,3-propylene sulfate (I) > 1,3-butylene sulfate > 1,4-butane sulfone > 1,2-ethylene sulfate (III) > diethyl sulfate > dimethyl sulfate. Dose-response studies indicated a linear dose-dependence of mutagenicity. In a repair test with *Proteus mirabilis* mutants defective in DNA repair, I and II showed DNA-damaging activity, but not ester III. (26 refs.)

78-1947 **Effects of Dietary Butylated Hydroxytoluene (BHT) on 2-Aminofluorene (AF) Activation and DNA Synthesis in Rat Lung and Liver (Meeting Abstract).** (Eng) Saccone, G. T. (Food Res. Inst., Dept. Food Microbiology and Toxicology, Univ. Wisconsin, Madison, WI, 53706); Pariza, M. W. *Proc Am Assoc Cancer Res* 19: 32; 1978. (no refs)

78-1948 **Effect of Antioxidants on Mutagenesis Induced by  $\beta$ -Propiolactone and Malonaldehyde (Meeting Abstract).** (Eng) Shamberger, R. J. (Cleveland Clinic Foundation, Cleveland, OH, 44106); Corlett, C. L.; Beaman, K. D.; Kasten, B. L. *Proc Am Assoc Cancer Res* 19: 48; 1978. (no refs)



78-1949 Sex-specific Protection by Antioxidant Butylated Hydroxytoluene (BHT) upon 1,2 Dimethylhydrazine (DMH) Colon Carcinogenesis in BALB/c Mice (Meeting Abstract). (Eng) Clapp, N. K. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Satterfield, L. C.; Bowles, N. D.; Klima, W. C. *Proc Am Assoc Cancer Res* 19: 65; 1978. (no refs)

78-1950 N-Hydroxy N-Glucuronic Acid Conjugates of Aromatic Amines and Their Role in Bladder Cancer Induction (Meeting Abstract). (Eng) Poupko, J. M. (Univ. Miami, Sch. Medicine, Miami, FL, 33152); Moreno, H. R.; Radomski, J. L. *Proc Am Assoc Cancer Res* 19: 141; 1978. (2 refs)

78-1951 Mutagenesis of Dapsone and its Derivatives in *Salmonella typhimurium* (Meeting Abstract). (Eng) Peters, J. H. (SRI International, Menlo Park, CA, 94025); Gordon, G. R.; Simmon, V. F.; Tanaka, W. *Fed Proc* 37(3): 450; 1978. (no refs)

78-1952 Mutagenic Potential and Influence on Cell Growth of Single Constituents of Dental Polymers (Meeting Abstract). (Eng) Hensten-Pettersen, A. (Scandinavian Inst. Dental Materials, Oslo, Norway); Jacobsen, N.; Jonsen, J. *J Dent Res* 57(A): 297; 1978. (1 ref)

78-1953 Effect of Various Factors on the Induction of Liver Tumors in Animals by Quinoline. (Eng) Shinohara, Y. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Ogiso, T.; Hananouchi, M.; Nakanishi, K.; Yoshimura, T.; Ito, N. *Gann* 68(6): 785-796; 1977.

The tumorigenic effect of a diet containing quinoline (Q) on the liver of various animals and the synergistic or antagonistic effect of other chemicals on quinoline hepatocarcinogenesis in rats were examined. 4,4'-Diaminodiphenylmethane (0.1%) and 3-methylcholanthrene (0.0067%) significantly inhibited Q-induced liver carcinogenesis in rats, but 1-naphthyl isothiocyanate (0.06%) and p-hydroxypropiophenone (1.0%) had no inhibitory effect. Transmission electron microscopy demonstrated the fine structure of the vascular tumors induced by Q. Although the compound was hepatocarcinogenic for mice and rats of both sexes, it did not induce liver tumors in hamsters or guinea pigs. Male rats were more susceptible than females, and mice showed the least susceptibility. The liver tumors of rats or mice were classified as heman-

gioendotheliomas, hemangiosarcomas, and hepatocellular carcinomas. Several treated rats had hemangiosarcomatous metastatic foci in their lungs. (38 refs)

78-1954 Effect of Tryptophan and Metabolites on Liver Azo Dye Reductase (Meeting Abstract). (Eng) Mostafa, M. H. (NCI, Bethesda, MD, 20014); Evans, R. P.; Weisburger, E. K. *Proc Am Assoc Cancer Res* 19: 178. (1 ref)

78-1955 Enzyme-altered Foci in Rat Liver Following Administration of Strong and Weak Hepatocarcinogens With and Without Phenobarbital (Meeting Abstract). (Eng) Pitot, H. C. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706); Kitagawa, Barsness, L. *Proc Am Assoc Cancer Res* 19: 209; 1978. (no refs)

78-1956 Modifications of 3'-Methyl dimethylaminoazobenzene Carcinogenesis in Rat Liver and Carcinogen Metabolism by Portacaval Anastomosis. (Eng) Ricco, J. B. (Laboratoire de Chirurgie Experimentale, INSERM U-17 et Universite Paris-Sud, Hopital Paul Brousse, 14, avenue Paul Vaillant-Couturier, 94800 Villejuif, France); Franco, D.; Morel, J.; Decloitre, F.; Bismuth, H. *Cancer Res* 37(12): 4505-4505; 1977

The effect of a portacaval shunt on hepatocarcinogenesis studied in Sprague-Dawley rats fed 0.07% 3'-methyl dimethylaminoazobenzene (3'-MeDAB) for 10 weeks. Portacaval anastomosis inhibited hepatocarcinogenesis as reflected by a delay of early-appearing  $\alpha$ -fetoprotein and an absence of late-appearing  $\alpha$ -fetoproteins, and a significantly lower tumor incidence than that in non-shunted rats. Reduction of hepatocarcinogenesis in shunted rats was associated with a decreased binding of 3'-MeDAB metabolites to liver proteins. This effect seemed to be related to modifications of the metabolic pathways of the carcinogen. Although the detoxifying azoreductase activity was not affected by portal diversion, the activating pathway leading to the binding of DAB metabolites to DNA, a major transformation step that is mediated by microsomal enzymes, was decreased in shunted rats to about 50% of control values. A marked decrease in liver tumor incidence in the shunted rats resulted in decreased DAB activation, but it did not modify the total detoxifying activity of the liver. This could be a direct consequence of portacaval anastomosis, as has been shown for other microsomal enzymes. (23 refs.)



1957 **Interaction of p-Dimethylaminoazobenzene with Rat Liver Chromatin and Nonhistones.** (Eng) Sonnenbichler, J. (Max-Planck-Institut für Biochemie, D-8033 Martinsried, W. Germany); Reichhart, F. *Z Krebsforsch* 91(1): 55-61; 1978.

The binding of tritiated p-dimethylaminoazobenzene (DAB) and p-aminazobenzene (AB) and their metabolites in liver chromatin was studied following the ip administration of 50 Ci of each compound to male Wistar rats. The amounts of DAB and its metabolites and of AB and its metabolites found in hepatocyte nuclei were  $99.1 \pm 6.3$  and  $47.2 \pm 3.6$  picomoles (pmol), respectively, vs  $42.6 \pm 2.1$  and  $14.8 \pm 0.8$  pmol in the total chromatin,  $11.7 \pm 0.6$  and  $5.8 \pm 0.5$  pmol in the total chromosomal protein,  $<0.1$  and  $<0.25$  pmol in the histones,  $4 \pm 0.8$  and  $<0.25$  pmol in the nonhistones, and  $3.9 \pm 1.6 \pm 0.1$  pmol in the nucleic acids. The findings indicate a considerable difference in the binding affinity of the two compounds to the nuclear nonhistone protein, and they support the hypothesis concerning the major role of nuclear nonhistones in the malignant transformation of liver cells. (23 refs)

1958 **Comutagenic Actions of Norharman Derivatives with 4-Dimethylaminoazobenzene and Related Compounds.** (Eng) Nagao, M. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1, Chuo-ku, Tokyo 104, Japan); Yahagi, T.; Honda, M.; Seino, Y.; Kawachi, T.; Shimura, T.; Wakabayashi, K.; Tsuji, K.; Kosuge, T. *Cancer Res* 35(5/6): 339-346; 1977.

The comutagenic activity of norharman (NH) with 4-dimethylaminoazobenzene (DAB) and its derivatives was investigated using *Salmonella typhimurium* strains TA98 and TA100. In all experiments, the medium was supplemented with the S9 fraction from the liver of Sprague-Dawley rats, NADPH, NADH, and ATP. NH (0-1 mg/plate) increased the mutagenic activity of 50  $\mu$ g DAB on TA98; NH alone had no mutagenic activity, and DAB alone was only weakly mutagenic. NH (0.2-1.0 mg/plate) scarcely affected the mutagenicity of DAB on TA100. At a concentration of 200  $\mu$ g/tube, NH enhanced the mutagenicities of 4-methylaminoazobenzene, 3'-methyl-4'-dimethylaminoazobenzene, 4-aminazobenzene, and 4'-methoxycarbonyl-N-hydroxy-4-methylaminoazobenzene. NH was thus a comutagen for these compounds; the metabolic activation system was necessary for the comutagenic action. The derivatives dihydro-NH, tetrahydro-NH, 9-methylcarboline, harman, and tetrahydroharman did not enhance the mutagenicity of DAB. (8 refs)

1959 **The Effect of Naphthalene Derivatives on Mitochondrial Metabolism and Chemical Oncogenesis in Culture (Meeting Abstract).** (Eng) Nesnow, S. (Bio-

chemistry Branch, Environmental Protection Agency, Research Triangle Park, NC, 27711). *Proc Am Assoc Cancer Res* 19: 75; 1978. (no refs)

78-1960 **Effect of Intestinal Bacteria on 3,2'-Dimethyl-4-aminobiphenyl (DMAB)-induced Carcinogenesis in Rats (Meeting Abstract).** (Eng) Reddy, B. S. (Naylor Dana Inst., American Health Foundation, Valhalla, NY, 10595); Watanabe, K.; Weisburger, J. H. *Proc Am Assoc Cancer Res* 19: 122; 1978. (no refs)

78-1961 **The Effects of Disulfiram (DSF) on the Carcinogenicity of 3,2'-Dimethyl-4-aminobiphenyl (DMAB) (Meeting Abstract).** (Eng) Fiala, E. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Son, O. S.; Weisburger, J. H. *Proc Am Assoc Cancer Res* 19: 66; 1978. (2 refs)

78-1962 **Effect of Phorbol Myristate Acetate on Cyclic Nucleotide Levels in Normal and Stimulated Mouse Epidermis In Vivo (Meeting Abstract).** (Eng) Garte, S. J. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016); Troll, W.; Belman, S. *Proc Am Assoc Cancer Res* 19: 7; 1978. (no refs)

78-1963 **Tumor Promoting Phorbol Esters Induce Anchorage Independent Growth in Some Epidermal Cell Strains (Meeting Abstract).** (Eng) Colburn, N. H. (NCI, Bethesda, MD, 20014); Former, B.; Warren, L. *Proc Am Assoc Cancer Res* 19: 65; 1978. (1 ref)

78-1964 **Induction of Ornithine Decarboxylase (ODC) Activity in Mouse Epidermis by 12-O-Tetradecanoylphorbol-13-acetate (TPA): Possible Involvement of Prostaglandins (Meeting Abstract).** (Eng) Verma, A. K. (McArdle Lab., Univ. Wisconsin, Madison, WI, 53706); Rice, H. M.; Ashendel, C. L.; Boutwell, R. K. *Proc Am Assoc Cancer Res* 19: 232; 1978. (no refs)

78-1965 **Regulation of Tumor Promoter Stimulated Ornithine Decarboxylase Activity and Thymidine Incorporation in Primary Mouse Epidermal Cell Cultures (Meeting Abstract).** (Eng) Lichti, U. (NCI, Bethesda, MD, 20014); Ben, T.; Patterson, E. *Proc Am Assoc Cancer Res* 19: 101; 1978. (no refs)



**78-1966 Metabolism of Phorbol Diesters by Cells in Culture (Meeting Abstract).** (Eng) O'Brien, T. G. (Wistar Inst., Philadelphia, PA, 19104); Diamond, L. *Proc Am Assoc Cancer Res* 19: 121; 1978. (no refs)

**78-1967 Phorbol Esters Produce a Delay in the Expression of Melanogenesis by B-16 Melanoma Cells (Meeting Abstract).** (Eng) Mufson, R. A. (Inst. Cancer Res., Columbia Univ., New York, NY, 10032); Fisher, P. B.; Weinstein, I. B. *Proc Am Assoc Cancer Res* 19: 183; 1978. (no refs)

**78-1968 Inhibition of the Mixed Lymphocyte Proliferative Response by Phorbol Esters.** (Eng) Mastro, A. M. (Dept. Biochemistry and Biophysics, Pennsylvania State Univ., 618 Life Sciences Building, University Park, PA, 16802); Mueller, G. C. *Biochim Biophys Acta* 517(1): 246-254; 1978.

The phorbol diester 12-O-tetradecanoyl-phorbol-13-acetate ( $10^{-7}$  or  $10^{-8}$  M), a potent cocarcinogen in mice, blocked the induction of DNA synthesis in bovine retropharyngeal lymphocytes undergoing the mixed lymphocyte response (MLR). At  $10^{-7}$  M diester, the induced DNA synthesis was inhibited by 99%. Phorbol 12,13-diacetate, a less potent analog in tumor promotion in vivo, was also a less potent inhibitor of the MLR (75% inhibition at  $10^{-6}$  M). Phorbol, the parent alcohol, is not effective in either system. The use of phorbol diesters in analyzing the molecular processes that control the MLR is discussed. This diester was effective when added as late as day 2 after the start of mixed lymphocyte cultures, implying that an early but not initial step in the cell replication process was affected; ongoing DNA synthesis was not significantly inhibited. (21 refs)

**78-1969 Mutagenicity Tests with Metrifonate in *Drosophila melanogaster*.** (Eng) Lamb, M. J. (Dept. Zoology, Birkbeck Coll., Malet St., London WC1E 7HX, England). *Mutat Res* 56(2): 157-162; 1977.

The mutagenicity of O,O-dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (metrifonate, trichlorfon, or Difterex) was examined in *Drosophila melanogaster*. Doses in toxicity tests ranged from 2.5 to 250 ppm; a dose of 15 ppm was used in the mutagenicity tests. The LD50 for death within 24 hr of feeding was 7 mg/kg. An av dose of 3.7 mg/kg was lethal to approx 20% of the flies within 1 day. Mutation experiments revealed no mutagenic effects, but only low concentrations of the compound were used because of its high toxicity. (10 refs)

**78-1970 Induction of Plasminogen Activator in Cultured Cells by Macrocyclic Plant Diterpene Esters and Other Agents Related to Tumor Promotion.** (Eng) Gler, M. (Inst. Cancer Res., Dept. Microbiology, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032); DeFeo, D.; Weinstein, I. B. *Cancer Res* 38(5): 1434-1438; 1978.

Since the tumor promotor phorbol-12-myristate-13-acetate induces the synthesis of plasminogen activator in cultured chick embryo fibroblasts, various compounds were tested for similar activity. Phorbol esters and other macrocyclic diterpene esters isolated from species of the plant families Euphorbiaceae and Thymelaeaceae were potent inducers of plasminogen activator. Compounds from these two families have been identified as antileukemic principles. They maximally induced enzyme to the same levels, although they differed in their relative molar potencies. Structural requirements for *in vitro* activity paralleled the requirements for *in vivo* activity. Tumor-promoting agents such as anthralin, cantharidin, Tween 60, and tobacco leaf extract failed to induce plasminogen activator. Thus, plasminogen activator induction is a useful marker for biologically active macrocyclic diterpene esters. (33 refs)

**78-1971 Chemical Ionization Mass Spectrometry of Tumor Promoter Related 4 $\alpha$ -Phorbol Esters.** (Eng) Solomon, J. J. (Lab. Organic Chemistry and Cancer Research, Inst. Environmental Medicine, New York Medical Center, New York, NY, 10016); Van Duuren, W.; Tseng, S. S. *Biomed Mass Spectrom* 5(2): 164-169; 1978.

The isobutane chemical ionization mass spectra of a series of 4 $\alpha$ -phorbol esters, including the tumor promoter phorbol-12-myristate-13-acetate, were determined. This technique allowed the identification of a series of substituted esters that were synthesized to study the effect of structure and stereochemistry on tumor promotion. (37 refs)

**78-1972 On the Metabolic Activation of Methylchrysene (Meeting Abstract).** (Eng) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, National Cancer Institute, Bethesda, MD, 20895); LaVoie, E. J.; Mazzarese, R.; Hoffmann, D. *Proc Am Assoc Cancer Res* 19: 116; 1978. (no refs)

**78-1973 Evidence that Bay Region Diol Epoxides of Chrysene and Dibenzo(a,h)anthracene are Ultimate Carcinogens (Meeting Abstract).** (Eng) A. W. (Hoffmann-La Roche, Inc., Nutley, NJ, 07110); W.; Chang, R. L.; Karle, J. M.; Mah, H. D.; Yagi, H.;



J. M.; Conney, A. H. *Proc Am Assoc Cancer Res* 19: 108; 1978. (no refs)

8-1974 **Prostaglandin Synthetase Dependent Benzo(a)-pyrene Oxidation (Meeting Abstract).** (Eng) Barnett, L. J. (Dept. Chemistry, Wayne State Univ., Detroit, MI, 48202); Reed, G. A.; Johnson, J. T. *Proc Am Assoc Cancer Res* 19: 25; 1978. (no refs)

8-1975 **Particle-mediated Membrane Uptake of Chemical Carcinogens Studied by Fluorescence Spectroscopy.** (Eng) Lakowicz, J. R. (Freshwater Biological Inst., Univ. Minnesota, Navarre, MN, 55392); McNamara, M.; Teenson, L. *Science* 199(4326): 305-307; 1978.

Because particulates and polynuclear aromatic hydrocarbons act as cocarcinogens, the uptake rate of chrysene, N-methylcarbazole and 1,6-diphenylhexatriene from particulates and into phospholipid vesicles was studied by fluorescent emissions. Chrysene entered phospholipid bilayers much more rapidly from the silica-absorbed state than from a microcrystalline state. The fluorescence emissions of N-methylcarbazole and 1,6-diphenylhexatriene also underwent large spectral shifts and/or changes in quantum yield upon uptake of the compounds from particulates by phospholipid vesicles. 1,6-Diphenylhexatriene was nonfluorescent on glass slides but highly fluorescent after transport into lipid vesicles. These findings indicate the feasibility of using fluorescence spectroscopy to measure the rates of exchange of polynuclear aromatic hydrocarbons from particulate matter to cell membranes. (14 refs)

8-1976 **The Interaction of Benzo(a)pyrene and Benzo(e)pyrene in Respiratory Tract Carcinogenesis (Meeting Abstract).** (Eng) Topping, D. C. (Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Pal, B.; Nettesheim, P. *Proc Am Assoc Cancer Res* 19: 43; 1978. (1 ref)

8-1977 **Binding of 6-Acetoxyethylbenzo(a)pyrene and ATP Mediated Binding of 6-Hydroxymethylbenzo(a)pyrene to DNA (Meeting Abstract).** (Eng) Tay, L. K. (Univ. Kentucky, Lexington, KY, 40506); Gydnor, K. L.; Flesher, J. W. *Proc Am Assoc Cancer Res* 19: 81; 1978. (no refs)

8-1978 **Morphology, Growth, and Metabolism of Chemical Carcinogens by Hepatocytes Main-**

**tained In Vitro on Plastic and Feeder Cells (Meeting Abstract).** (Eng) Tompa, A. (Eppley Inst. Cancer Res., Univ. Nebraska Medical Center, Omaha, NB, 68105); Huberman, E.; Langenbach, R. *Proc Am Assoc Cancer Res* 19: 185; 1978. (no refs)

78-1979 **Simultaneous Determination of the Cytotoxic, Mutagenic and Transforming Activities of Benzo(a)pyrene (BP) Metabolically Activated In Vitro (Meeting Abstract).** (Eng) Schechtman, L. M. (Dept. Biochemical Oncology, Microbiological Associates, Bethesda, MD, 20016); Beard, S.; Dively, C.; Joglekar, R.; Slomiany, D. *Proc Am Assoc Cancer Res* 19: 142; 1978. (no refs)

78-1980 **Non-enzymic Activation of Polycyclic Aromatic Hydrocarbons as Mutagens.** (Eng) Gibson, T. L. (Dept. Human Biological Chemistry and Genetics, Div. Biochemistry, Univ. Texas Medical Branch, Galveston, TX, 77550); Smart, V. B.; Smith, L. L. *Mutat Res* 49(2): 153-161; 1978.

Twenty-two <sup>60</sup>Co γ-irradiated polycyclic aromatic hydrocarbons (PAH) and their related derivatives were tested for mutagenicity using *Salmonella typhimurium* strains TA98, TA1535, TA1537, and TA1538. No hepatic S-9 mix or other activating systems were added to the bacterial strains. Marked mutagen responses were obtained for several irradiated samples with TA98, TA1537, and TA1538, but not with TA1535. Irradiated samples of benzo(a)anthracene, benzanthrone, benzo(g,h,i)perylene, benzo(a)pyrene, chrysens, fluorene, 9-methylanthracene, 1-methylphenanthrene, 2-methylphenanthrene, and pyrene gave positive mutagenic tests and dose responses, but the unirradiated control samples of these compounds were inactive. Acenaphthene, phenanthrene, and phenanthrenequinone exhibited toxicity that interfered with interpretation of the testing. Samples of 2-methylanthracene and tetracene were mutagenic with or without irradiation. Alizarin, anthracene, anthraquinone, anthrone, dibenzo(a,h)anthracene, picene, and triphenylene gave negative results. Samples of benzo(a)pyrene adsorbed on silica gel irradiated in air by <sup>60</sup>Co or by UV light (254 nanometers) produced preparations mutagenic toward TA98, TA1537, and TA1538. Thus, parent PAH not themselves mutagenic toward *S. typhimurium* may be oxidized in air by radiation-induced processes to products whose mutagenicity resembles that of the liver-microsomal metabolites of the parent PAH. (12 refs)

78-1981 **Human Bronchus-mediated Mutagenesis Assay in Mammalian Cells (Meeting Abstract).** (Eng) Hsu, I. C. (Human Tissue Studies Section, Experimental Pathology Branch, NCI, Bethesda, MD, 20014); Trump,



B. F.; Saffiotti, U.; Harris, C. C. *Proc Am Assoc Cancer Res* 19: 78; 1978. (no refs)

**78-1982 Uptake of Benzo(a)pyrene (BP) and Release of Mutagenic Metabolites by Cultured Human Pulmonary Alveolar Macrophages (PAM) (Meeting Abstract).** (Eng) Harris, C. C. (Human Tissues Study Section, Experimental Pathology Branch, NCI, Bethesda, MD, 20014); Autrup, H.; Stoner, G.; Trump, B. F. *Proc Am Assoc Cancer Res* 19: 119; 1978. (no refs)

**78-1983 Uptake Metabolism and Excretion of Benzo(a)-pyrene and its Metabolites by the Rat Pancreas (Meeting Abstract).** (Eng) Iqbal, Z. M. (Environmental and Occupational Medicine, Sch. Public Health, Univ. Illinois Medical Center, Chicago, IL, 60680); Yoshida, A.; Epstein, S. S. *Proc Am Assoc Cancer Res* 19: 5; 1978. (no refs)

**78-1984 Relationship Between Biological Activity and Metabolism of Polycyclic Hydrocarbon Carcinogens in Cultured Fibroblasts from Various Mammalian Species (Meeting Abstract).** (Eng) Moore, C. J. (Dept. Microbiology and Fels Res. Inst., Temple Univ. Medical Sch., Philadelphia, PA, 19140); Schwartz, A. G. *Proc Am Assoc Cancer Res* 19: 103; 1978. (no refs)

**78-1985 Divergence of Metabolic Activation Systems for Short-term Mutagenesis Assays.** (Eng) Selkirk, J. K. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830). *Nature* 270(5638): 604-607; 1977.

The metabolism of benzo(a)pyrene (BP) was compared in liver microsomes from male Sprague-Dawley rats and Syrian Golden hamsters, hamster embryo cells and hamster embryo cell microsomes. Monooxygenases were induced by ip injection of 5 mg methylcholanthrene 40 hr before killing. Rat and hamster liver microsomes had metabolite patterns containing 9,10-, 4,5-, and 7,8-dihydro-dihydroxy-BP, 1,6', 3,6'- and 6,12-BP quinone and 9-OH and 3-OH-BP. Liver contained the highest level of the drug metabolizing enzymes; hamster liver produced almost exclusively the 4,5-diol while this was a lesser component of rat liver metabolites. Microsomes from hamster cells either produced insignificant amounts of or further metabolized the diols and quinones forming 9-hydroxy-BP as the major product. In intact hamster cells, the 9,10- and 7,8-diols were the major products. If activation of specific regions of the carcinogen is more important than other regions in tumorigenesis, then in vitro mutagenesis assays must closely approximate the in vivo situation. In vitro

assays using intact cell feeder layers as activation systems for producing reactive carcinogens for test cell cultures appear to be the best system for in vivo comparisons (23 refs.)

**78-1986 Benzo(a)pyrene Metabolism (BP) in Primary Hepatocytes and Normal and Transformed Epithelial Cells (Meeting Abstract).** (Eng) Selkirk, J. K. (Oak Ridge Natl. Lab., Oak Ridge, TN); Huisingh, J.; Montes, R. *Proc Am Assoc Cancer Res* 19: 23; 1978. (no refs)

**78-1987 Highly Purified Cytochrome P-450 LM's Bound to Different Extents During the Metabolism of (-)trans-7,8-Dihydroxy-7,8-dihydrobenzo(a)pyrene (Meeting Abstract).** (Eng) Deutsch, J. (NIH, Bethesda, MD, 20014); Leutz, J. C.; Coon, M. J.; Vatsis, K. P.; Chiang, L.; Gelboin, H. V. *Proc Am Assoc Cancer Res* 19: 77; 1978. (no refs)

**78-1988 Metabolic Activation of 7,8-Dihydroxy-7,8-dihydrobenzo(a)pyrene by Lung and Liver Microsomes of C57BL/6, C3H, and DBA/2 Strains of Mice (Meeting Abstract).** (Eng) Wang, I. Y. (Medical Univ. of South Carolina, Charleston, SC, 29403). *Proc Am Assoc Cancer Res* 19: 20; 1978. (no refs)

**78-1989 A Comparison of the Effect of BP 4,5-Oxidation by N-AcO-AAF on Repair Replication and DNA Synthesis in Human Cells (Meeting Abstract).** (Eng) Mick, J. J. (Michigan State Univ., East Lansing, MI, 48824); Levinson, J. W.; Maher, V. M. *Proc Am Assoc Cancer Res* 19: 71; 1978. (no refs)

**78-1990 The Effect of Cytochrome P-450-448 Inhibitors on the Binding of Benzo(a)pyrene and Derivatives to DNA upon Microsomal Activation (Meeting Abstract).** (Eng) Liu, W.-I. (Dept. Biochemistry, Univ. Tennessee Center Health Sciences, Memphis, TN, 38163); Selkirk, J. K. *Proc Am Assoc Cancer Res* 19: 38; 1978. (3 refs)

**78-1991 DNA and RNA Adducts Formed in Hamster Embryo Cell Cultures Exposed to Benzo(a)pyrene (BP) (Meeting Abstract).** (Eng) Ivanovic, V. (Institute of Cancer Res., Columbia Univ., New York, NY, 10032); J.



M.; Weinstein, I. B. *Proc Am Assoc Cancer Res* 19: 183; 1978. (no refs)

1992 On the Biochemical Mechanism of Tumorigenesis in Mouse Skin. VIII. Isolation and Characterization of Epidermal Microsomes and Properties of Their Arylhydrocarbon Monooxygenase and Epoxide Hydratase. (Eng) Pyerin, W. G. (Deutsches Krebsforschungszentrum Heidelberg, Im Neuenheimer Feld 280, D-6900 Heidelberg, Germany); Hecker, E. *Z Krebsforsch* 90(3): 259-279; 1978. (no refs)

Epidermal microsomes were isolated from mouse skin and arylhydrocarbon monooxygenase (AHM) and epoxide hydratase (EH) activities studied. Epidermal scrapings were homogenized and then subjected to differential centrifugation to yield a microsomal pellet having AHM activities two to three times higher and EH activities six to eight times higher than those in the homogenate. AHM activity was measured spectrophotometrically with the use of benzo(a)pyrene (BP) as the substrate. The fluorometric spectrum of the polar metabolites of BP was similar to that generated in assays using liver microsomes and to that of standard 3-hydroxybenzo(a)pyrene. There was no change in the spectrum when microsomes from dimethylbenz(a)anthracene (DMBA)-treated mice were used. EH activity was measured using styrene oxide as the substrate. In both assays, there was linearity of product formation with the incubation times and protein concentrations and saturation of enzyme by the substrate concentration was observed. The results demonstrate the presence of both enzymes in the dorsal epidermis of mice. From the influence of the selective inhibitors SKF 525-A and 7,8-benzoflavone on the activity of epidermal AHM in vitro, it is concluded that in epidermis this enzyme contains both cytochrome P-450 and cytochrome P-448. (59 refs)

1993 Benzo(a)pyrene and 7,12 Dimethylbenz(a)anthracene Adducts in Mouse Epidermal DNA. (Meeting Abstract). (Eng) Pereira, M. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Burns, F. J.; Albert, R. E. *Proc Am Assoc Cancer Res* 19: 207; 1978. (no refs)

1994 DNA Postreplication Repair Induced by Benzo(a)pyrene Diol Epoxide in Primary Mouse Epidermal Cell Cultures (Meeting Abstract). (Eng) Bowden, J. (NIH, Bethesda, MD, 20014); Yuspa, S. *Proc Am Assoc Cancer Res* 19: 85; 1978. (no refs)

1995 Light, Cytotoxicity and Binding of Benzo(a)pyrene to Human Epithelial Cells in Culture

(Meeting Abstract). (Eng) Gantt, R. (NIH, Bethesda, MD, 20014); Camalier, R.; Price, F.; Taylor, W. G.; Sanford, K. K. *Proc Am Assoc Cancer Res* 19: 107; 1978. (no refs)

78-1996 Sustained-Release Implants of Chemical Carcinogens in the Canine Tracheobronchial Tree. (Eng) Matsumura, K. (Dept. Surgery, Harbor General Hosp. Campus, UCLA Sch. Medicine, Torrance, CA, 90502); Shors, E. C.; Fu, P. C.; Cohen, A. H.; Benfield, J. R. *Ann Thorac Surg* 25(2): 112-116; 1978.

Benzo(a)pyrene (BP) was incorporated into liquid silicone rubber, allowed to harden, and cut into disks (BP polymer) containing 9.05%-12.12% BP. These disks were sutured into the trachea and right main bronchus of dogs either by fixing the polymer directly to the epithelial surface (fixation method) or by implanting it into submucosal pockets (pocket method). Twenty-one polymer disks were implanted in 10 dogs. A total of 2/14 disks implanted by the fixation method were extruded; all 7 disks implanted by the pocket method remained in place 4-8 mo after surgery. Within 1 mo, the mucosa overlying the pocket implants was morphologically identical to the fixation implants. Squamous metaplasia was consistently found within the first postoperative week. Basal hyperplasia was regularly associated with the metaplasia induced by pocket implants; no basal metaplasia was noted with fixation implants. One dog developed atypical metaplasia with increased mitotic activity 5 mo after pocket implantation. No abnormalities have been noted in dogs receiving implants of solidified silicone rubber only. Long-term studies will determine whether lung cancer will be induced. (7 refs)

78-1997 Binding of Benzo(a)pyrene into Nuclear Subfractions in Rat Tissues (Meeting Abstract). (Eng) Hemminki, K. (Dept. Medical Chemistry, Univ. Helsinki, Helsinki 17, Finland); Blazsek, I.; Vauhkonen, M. *Proc Am Assoc Cancer Res* 19: 43; 1978. (no refs)

78-1998 On the Mechanism of Disulfiram Inhibition of Benzo(a)pyrene (BP) Induced Neoplasia in the Mouse Forestomach (Meeting Abstract). (Eng) Borchert, P. (Dept. Lab. Medicine, Univ. Minnesota, Minneapolis, MN, 55455); Galbraith, A.; Wattenberg, L. W. *Proc Am Assoc Cancer Res* 19: 61; 1978. (no refs)

78-1999 A Method for Experimental Induction of Bronchogenic Carcinoma in Subcutaneously Implanted Bronchial Autograft in Dogs. (Eng) Kobayashi, N. (Dept. Thoracic Surgery, Kenseibu Hamamatsu Medical



Center, 328 Tomitsuka-Cho, Hamamatsu 432, Japan); Okita, M.; Yarita, T.; Hanzawa, S.; Okamoto, T.; Katsuki, H. *J Thorac Cardiovasc Surg* 75(3): 434-442; 1978.

A method for the induction of bronchogenic carcinoma in dogs is presented, and the stages in tumorigenesis are listed. Sixteen mongrel dogs were anesthetized, and a free circumferential section was dissected from the main to the lower lobe bronchus. This graft was then inserted into the sc tissue of the back and, 4 wk later, 30, 50, or 90 mg 3-methylcholanthrene, or 30, 70, or 90 mg benzo(a)pyrene was injected into the lumen of the graft. Squamous metaplasia accompanied by hyperplasia was noted as early as 5 wk, and early invasive squamous cell carcinomas were noted in < 30 wk. Biopsy specimens indicated that the cancer progressed from mucosal hyperplasia to squamous metaplasia with moderate atypia, metaplasia with marked atypia, cancerous atypical cell proliferation, and invasive squamous cell carcinoma. (18 refs)

**78-2000 Determination of Benzo(a)pyrene Levels in the Air Around Madrid.** (Spa) de la Serna, J. (Departamento de Sanidad Ambiental, Escuela Nacional de Sanidad, Madrid, Spain); Caballero, F. *Rev Sanid Hig Publica (Madr)* 51(3/4): 265-309; 1977.

Benzo(a)pyrene (BP) levels in Madrid air were determined between 1969 and 1972. The particulate matter in the air was filtered and then extracted by an organic solvent, the components were separated by paper chromatography, and the BP concentration was determined by spectrofluorometry. During this period, the concentrations at various sampling points ranged from 0 to 178.4  $\mu\text{g}/1,000 \text{ m}^3$  air. (77 refs)

**78-2001 Evaluation of Exposure to Harmful Pollutants Emitted During the Production of Aluminum Using Self-baking Anodes.** (Pol) Adamiak-Ziemba, J. (Instytut Medycyny Pracy, ul. Bracka 55, 91-717 Lodz, Poland); Ciosek, A.; Gromiec, J. *Med Pr* 28(6): 481-489; 1977.

Two aluminum reduction plants that used selfbaking anodes for electrolysis were studied with respect to emissions of harmful airborne substances. Carbon monoxide, inorganic fluorides, coal tar volatiles, dust, and benzo(a)pyrene (BP) were identified as the principal air pollutants emitted in both plants. BP and other carcinogens present in the coal tar volatiles were found to be the major toxic substances emitted. The geometric mean concentrations of BP and the coal tar volatiles were 1.85  $\mu\text{g}/\text{m}^3$  and 0.49  $\text{mg}/\text{m}^3$  in plant A and 3.7  $\mu\text{g}/\text{m}^3$  and 0.65  $\text{mg}/\text{m}^3$  in plant B, respectively. The BP and coal tar volatile concentrations in the air of an anode-making room were 0.19-4.9  $\mu\text{g}/\text{m}^3$  and 0.16-1.4  $\text{mg}/\text{m}^3$ , respectively. (25 refs.)

**78-2002 Position-Sensing Proportional Counting: A Rapid Method for Quantitation of [ $^3\text{H}$ ]Benzo(a)pyrene Metabolites on Thin-Layer Chromatograms (Meeting Abstract).** (Eng) Baird, W. M. (Wistar Inst., Philadelphia, PA, 19104); Borun, T. W.; Shulman, S. D.; Leonard, L. *Proc Am Assoc Cancer Res* 19: 120; 1978. (no refs)

**78-2003 Deuteriodeprotonation of Benzo(rst)pentaphenyl (Dibenzo(ai)pyrene, DBP) and its Fluorinated Derivatives (Meeting Abstract).** (Eng) Sardella, D. J. (Chemistry Dept., Boston Coll., Chestnut Hill, MA, 02167); Mathalang, P.; Boger, E. *Proc Am Assoc Cancer Res* 19: 46; 1978. (1 ref)

**78-2004 Metabolic Formation of 1,9,10-Trihydroxy-9,10-dihydro-3-methylcholanthrene: A Potential Proximate Carcinogen from 3-Methylcholanthrene (Letter to Editor).** (Eng) Thakker, D. R. (Section on Oxidative Mechanisms, Lab. Chemistry, Natl. Inst. Arthritis, Metabolism, Digestive Diseases, NIH, Bethesda, MD, 20014); Levin, W.; Wood, A. W.; Conney, A. H.; Stoming, T. A.; Jerina, D. M. *J Am Chem Soc* 100(2): 645-647; 1978.

Four dihydrodiols were formed by the metabolism of hydroxy-methylcholanthrene in a purified monooxygenase system containing epoxide hydrolase. On the basis of its nuclear magnetic resonance spectrum, the major dihydrodiol was trans-9,10-dihydroxy-9,10-dihydro-1-hydroxymethylcholanthrene. Dihydrodiol has a bay-region double bond, indicating that it may be an ultimate carcinogenic metabolite. (19 refs.)

**78-2005 Nuclear Mixed Function Oxidase (MFO) Activity: Its Ontogeny and Immunology (Meeting Abstract).** (Eng) Bresnick, E. (Vermont Regional Cancer Center, Univ. Vermont Coll. Medicine, Burlington, VT, 05401); Nunnink, J. C.; Chuang, A. H.; Hassuk, B.; Borzak, D.; Levin, W.; Thomas, P. E. *Proc Am Assoc Cancer Res* 19: 50; 1978. (no refs)

**78-2006 Induction of Rat Liver Nuclear Cytochrome P-450 and Related Enzymes by Phenobarbital (PB) and 3-Methylcholanthrene (MC) (Meeting Abstract).** (Eng) Yang, C. S. (New Jersey Medical Sch., Newark, NJ, 07103); Kicha, L. P. *Proc Am Assoc Cancer Res* 19: 44; 1978. (1 ref)



2007 Pathogenesis of Chemically Induced Lung Lesions in Mice (Meeting Abstract). (Eng) Billups, I. (Microbiological Associates, Bethesda, MD, 20016); Fry, C. J.; Whitmire, C. E.; Kouri, R. E. *Proc Am Assoc Cancer Res* 19: 142; 1978. (no refs)

2008 Immunoprotective and Tumor Potentiating Fractions in 3M KCl Extracts of Murine Fibrosarcomas (Meeting Abstract). (Eng) Pellis, N. R. (Dept. Surgery, Univ. Texas Medical Sch., Houston, TX, 77030); Lan, D. J.; Wiseman, F. C.; Kahan, B.D. *Proc Am Assoc Cancer Res* 19: 139; 1978. (no refs)

2009 Evidence for Similar Principal Target Proteins of Chemical Carcinogens in Six Carcinogen-Sensitive Systems (Meeting Abstract). (Eng) Sorof, S. (Inst. Cancer Res., Philadelphia, PA, 19111); Dickens, M. S. *Proc Am Assoc Cancer Res* 19: 37; 1978. (1 ref)

2010 Differential Inhibition of Aryl Hydrocarbon Hydroxylase in Human Foetal Liver, Adrenal Gland and Placenta. (Eng) Pelkonen, O. (Dept. Pharmacology, Univ Oulu, SF-90220 Oulu 22, Finland). *Acta Pharmacologica (Kbh)* 41(4): 306-316; 1977.

The inhibition of aryl hydrocarbon hydroxylase (AHH) by various compounds was studied in the human fetal and adult liver, fetal adrenal gland, and placenta and in fetal and neonatal Sprague-Dawley rat tissues. Human fetuses were divided into two groups according to the smoking (or nonsmoking) habit of the mothers. There was substantial AHH activity in all human livers and adrenal glands, but only in term placentas from smoking mothers. Placental AHH was inhibited by 0.1 mM 7,8-benzoflavone (BF), but not appreciably by 0.2 mM SKF 525A or 10 mM aminopyrine (AP). The fetal hepatic system was inhibited 46% by SKF 525A and 79% by AP, but it was activated 100% by BF. The results were similar in adult liver AHH. Fetal adrenal gland AHH was inhibited by AP, and only in fetuses from smokers. In general, however, maternal cigarette smoking did not have any appreciable effects on AHH activity or its inhibitory properties. The rats were treated with 3-methylcholanthrene (3-MC: 20 mg/kg for 3 days ip) or sesame oil and sacrificed 24 hr later. The inhibitory properties of control rat hepatic AHH resembled those of human fetal hepatic AHH; the inhibitory properties of treated rat hepatic AHH resembled those of human placenta AHH. The effect of BF on control rat hepatic AHH activity varied greatly from the prenatal to the adult period, but AHH activity in 3-MC-treated rat liver was always strongly inhibited by BF. Spectral studies of micro-

somes showed no great differences between smokers and nonsmokers in cytochrome P-450 content or in location of the spectral max in the CO-induced difference spectrum. However, there were large differences in cytochrome P-450 content among all the different human and rat tissues. (24 refs)

78-2011 Inhibition In Vitro of 3-Methylcholanthrene (MCA)-induced Malignant Transformation of C3H/10T1/2 CL8 (10T1/2) Mouse Fibroblasts by Retinoids (Meeting Abstract). (Eng) Merriman, R. L. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263); Bertram, J. S. *Proc Am Assoc Cancer Res* 19: 236; 1978. (no refs)

78-2012 Unscheduled DNA Synthesis in Cultured Human Skin Epithelium (Meeting Abstract). (Eng) Lake, R. S. (Children's Hosp. Medical Center, Akron, OH, 44308); Shoemaker, R. H.; Igel, H. J. *Proc Am Assoc Cancer Res* 19: 21; 1978. (no refs)

78-2013 Extractable Collagenase and Carcinogenesis of the Mouse Skin. (Eng) Wirl, G. (Institut für Molekularbiologie der Österreich, Akademie der Wissenschaften, Abteilung Biologie, A 5020 Salzburg, Austria). *Connect Tissue Res* 5(3): 171-178; 1977.

The presence of extractable collagenase in mouse skin during carcinogenesis was examined. Female, outbred, Swiss albino mice received topical application of 0.5 mg 3-methylcholanthrene (3-MC) in 0.2 ml acetone twice weekly for 20 wk. Collagen content decreased and reached a minimum (89 mg/g dry wt) at approx 5 wk; it then increased to about 120 mg/g dry wt and remained at this level for 10 wk. Extraction of collagenase 72 hr after the last application failed to demonstrate a stimulating effect of 3-MC on extractable enzyme. In short-term experiments, mice received the same dose at 2-day intervals for 2, 3, 4, or 6 applications, and the skin was excised 12, 24, and 48 hr later. High collagenase levels were recovered after three applications; enzyme activity peaked at 24 hr and returned to normal by 48 hr. Extractable enzyme was reduced below control values after four treatments, and it was not measurable after two or six treatments. Hydroxyproline assays revealed that the low collagen levels obtained after 2, 3, or 4 treatments were almost restored 36 hr later. Only the collagen of skins treated six times reverted to a low level after a brief rise at 24 hr. 3-MC was then administered as a 0.5% soln in benzene and painted on the skin three times per week. The response of extractable collagenase activity to 3-MC dissolved in benzene differed from that to 3-MC in acetone in two respects: peak activity with the benzene vehicle was later, and the peak



was broader. Levels of extractable enzyme were affected by benzene alone. Repeated 3-MC applications resulted in benign papillomas and malignant carcinomas. Enzyme activity in the 6000 x g pellet was higher than that of the supernatant for benign and malignant tumors. Although enzyme activity was elevated in both tumor types, that in the carcinomas was profoundly higher. There was no correlation between collagen content and amount of extractable enzyme. (41 refs.)

- 78-2014 Aryl-Hydrocarbon-Hydroxylase Inducibility in Patients with Cancer.** (Eng) Emery A. E. (Univ. Dept. Human Genetics, Western General Hosp., Edinburgh, Scotland); Danford, N.; Anand, R.; Duncan, W.; Paton, L. *Lancet* 1(8062): 470-472; 1978.

Aryl hydrocarbon hydroxylase (AHH) inducibility was studied in the peripheral blood lymphocytes of patients with squamous cell lung cancer, patients with various other cancers (colorectal, pancreatic, and prostatic cancer), and controls matched for age, sex, social class, and smoking habits. All individuals in the study had smoked at least 20 cigarettes/day for at least 10 yr up to within a short time of the investigation. Phytohemagglutinin-stimulated lymphocytes were exposed to benzantracene (BA), and AHH activity was determined. Inducibility was expressed as the ratio of activity in the presence and absence of BA. The proportion of high inducers was significantly greater among patients with lung cancer (but not patients with other cancers) than among controls, suggesting that, besides smoking, a constitutional factor may be involved in the pathogenesis of lung cancer. (16 refs)

- 78-2015 Immunogenicity of Preneoplastic and Neoplastic Mammary Lesions. Relationship to the Presence of Chemical Carcinogens (Meeting Abstract).** (Eng) Wei, W. Z. (Div. Biology and Medicine, Brown Univ., Providence, RI, 02912); Medina, D.; Heppner, G. H. *Proc Am Assoc Cancer Res* 19: 59; 1978. (no refs)

- 78-2016 Aryl Hydrocarbon Hydroxylase (AHH) Activity in Mouse, Rat and Human Mammary Tumors (Meeting Abstract).** (Eng) Okey, A. B. (Univ. Windsor, Ontario, Canada); Mason, M. E. *Proc Am Assoc Cancer Res* 19: 29; 1978. (no refs)

- 78-2017 Comparison of Aryl Hydrocarbon Hydroxylase (AHH) Activity in Freshly Isolated and Cultured Rat Mammary Epithelial Cells (Meeting Abstract).** (Eng) Greiner, J. W. (NCI, Frederick Cancer Res. Center,

Frederick, MD, 21501); Malan, L. B.; Janss, D. H. *Proc Am Assoc Cancer Res* 19: 164; 1978. (no refs)

- 78-2018 Insulin-Estrogen Relationship and Hormonal Regulation of Growth of DMBA-induced Mammary Tumors (Meeting Abstract).** (Eng) Shafie, S. M. (Biochemistry Dept., Univ. Rochester Sch. Medicine, Rochester, NY, 14642); Hilf, R. *Proc Am Assoc Cancer Res* 19: 41; 1978. (no refs)

- 78-2019 Interaction of Cyclic AMP and Estrogen in Hormone Dependent Mammary Carcinoma (Meeting Abstract).** (Eng) Bodwin, J. (Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20014); Clair, T.; Cho-Chung, S. *Proc Am Assoc Cancer Res* 19: 124; 1978. (no refs)

- 78-2020 DNA Synthesis and Terminal End Bud Density in Mammary Gland as Determinants of Susceptibility to Carcinogens (Meeting Abstract).** (Eng) Russo, J. (Experimental Pathology Lab., Michigan Cancer Foundation, Detroit, MI, 48201). *Proc Am Assoc Cancer Res* 19: 22; 1978. (1 ref)

- 78-2021 Influence of Age on the Development of Mammary Carcinomas Induced with 7,12-Dimethylbenz(a)anthracene (DMBA): Relationship Between Mammary Dysplasia and Carcinoma Development (Meeting Abstract).** (Eng) Haslam, S. Z. (Cancer Res. Lab., Univ. California, Berkeley, CA, 94720). *Proc Am Assoc Cancer Res* 19: 186; 1978. (no refs)

- 78-2022 Effect of Feeding Unsaturated or Saturated Fats on Carcinogenesis on Mouse Skin (Meeting Abstract).** (Eng) Troll, W. (New York Univ. Medical Center, New York, NY, 10016); Belman, S.; Goldstein, B.; Mukherjee, F.; Machlin, L. *Proc Am Assoc Cancer Res* 19: 106; 1978. (no refs)

- 78-2023 The Effects of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Aroclor 1254 on 7,12-Dimethylbenz(a)anthracene Metabolism and Tumor Activity in Mouse Skin (Meeting Abstract).** (Eng) DiGiovanni, N. (Dept. Pharmacology, Univ. Washington, Seattle, WA, 98195); Slaga, T. J.; Berry, D. L.; Juchau, M. R. *Proc Am Assoc Cancer Res* 19: 110; 1978. (no refs)



78-2024 **Inhibition of Polycyclic Aromatic Hydrocarbon (PAH)-induced Neoplasia by Naturally Occurring Indoles (Meeting Abstract).** (Eng) Wattenberg, L. W. Univ. Minnesota, Minneapolis, MN, 55455; Loub, W. D. *Proc Am Assoc Cancer Res* 19: 36; 1978. (no refs)

8-2025 **The Developmental Stage of the Rat Mammary Gland as a Determinant of its Susceptibility to 7,12-Dimethylbenz(a)anthracene (Meeting Abstract).** (Eng) Russo, I. H. (Experimental Pathology Lab., Michigan Cancer Foundation, Detroit, MI, 48201). *Proc Am Assoc Cancer Res* 19: 228; 1978. (1 ref)

8-2026 **Origin of Tubular Complexes Developing During Induction of Pancreatic Adenocarcinoma by 7,12-Dimethylbenz(a)anthracene.** (Eng) Bockman, D. E. Dept. Anatomy, Georgia Medical Coll., Augusta, GA, 30902; Black, O.; Mills, L. R.; Webster, P. D. *Am J Pathol* 103: 645-659; 1978.

7,12-Dimethylbenz(a)anthracene (DMBA: 1-10 mg as crystals or in dextrose pellets) was implanted in the pancreas of Sprague-Dawley and Long-Evans rats, and the tubular complexes that appear during adenocarcinoma induction by DMBA were studied by light and electron microscopy. In addition, a tubular complex was reconstructed from serial sections to determine its three-dimensional configuration. Although tubular complexes have been thought to result from ductal proliferation, the following observations indicate that they originate from zymogen-granule-containing cells: (1) there was a continuum of transitional stages between acini and tubules; (2) most tubules decreased in size and were replaced by connective tissue (evidence of regression rather than proliferation); (3) few mitotic figures were seen in tubular complexes; (4) the tubules comprised many cells with an abundance of rough endoplasmic reticulum, an organelle that is sparse in ducts; and (5) the three-dimensional arrangement of tubules appeared identical to the branching, anastomosing arrangement of zymogen-granule-containing cells of the normal rat pancreas. Control animals who received only sutures in the pancreas showed minimal reaction. It is concluded that acini become recognized as tubules when loss of zymogen granules accompanies tumor induction by DMBA. Transformation of these cells could be interpreted erroneously as transformation from proliferating ducts. (18 refs)

8-2027 **Long-Term Action of 7,12-Dimethylbenz(a)anthracene (DMBA) on Pituitary and Adrenals in the Rat.** (Eng) Danguy, A. (Lab. Histology, Sch. Medicine, Universite Libre de Bruxelles, Brussels, Belgium); Heuson-Stiennon, J. A.; Toubreau, G.; Pasteels, J. L. *IARC Med Sci [Cancer]* 6(2): 79; 1978.

The long-term effects of a single dose of 7,12-dimethylbenz(a)anthracene were investigated in 15 female Sprague-Dawley rats fed 20 mg at the age of 50 days and sacrificed 150, 200, or 300 days later. There was a 100% incidence of mammary tumors, adrenal tumors, and tumors of the anterior lobe of the pituitary in the treated animals, but none of these tumors occurred in controls. The histology of the adrenal and pituitary tumors is described. (8 refs)

78-2028 **Morphological Features Altered with Increasing Oncogenic Potential of Respiratory Tract Epithelial Cell Lines (Meeting Abstract).** (Eng) Heckman, C. A. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Olson, A. C.; Marchok, A. C. *Proc Am Assoc Cancer Res* 19: 214; 1978. (no refs)

78-2029 **Effects of Aminophylline and Dibutyryl cAMP on Hamster Pouch Carcinogenesis (Meeting Abstract).** (Eng) Singh, B. B. (Medical Coll. Georgia, Augusta, GA, 30902); McKinney, R. V.; Allen, E.; Kolas, S. *J Dent Res* 57(A): 262; 1978. (no refs)

78-2030 **Effect of Pretreatment with  $\alpha$ -Naphthoflavone (ANF) and Nucleophiles on 7,12-Dimethylbenz(a)anthracene (DMBA) Toxicity and Death in DBA/2N (D2) and C57BL/6N (B6) Mice (Meeting Abstract).** (Eng) Mattison, D. R. (Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD, 20014). *Proc Am Assoc Cancer Res* 19: 45; 1978. (no refs)

78-2031 **Does Carcinogenic Potency Correlate With Mutagenic Potency in the Ames Assay?** (Eng) Ashby, J. (Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Nr Macclesfield, Cheshire, England); Styles, J. A. *Nature* 271(5644): 452-455; 1978.

Since the Ames *Salmonella* reverse mutation assay of the mutagenic potential of a compound is frequently interpreted as a measure of the compound's carcinogenicity, the value of this interpretation is discussed. Carcinogens are known to be species-specific, and a compound found to be carcinogenic by an in vitro test could subsequently be found to be noncarcinogenic in animal models. Furthermore, the rat hepatic S9 microsomal mix is used in the Ames assay, and for quantitative results, the enzyme composition of this mix should be determined. Addition of epoxide hydratase to the S9 mix abolishes the mutagenic response of benzo(a)pyrene (BP) by preventing the formation of the active species. As an example of the species specificity of the S9 mix, vinylidene dichloride



is mutagenic in the Ames assay when mouse S9 fractions are used, but it is nonmutagenic with rat S9 fractions. One species may possess enzymes capable of detoxifying the carcinogen but another may not, resulting in conflicting results. Experiments using the S9 fraction from Sprague-Dawley and Alderley Park rat livers and Alderley Park albino mouse and guinea pig livers (both induced and noninduced) indicated that only the guinea pig S9 fraction cannot activate BP to a mutagen because of epoxide-destroying species in the mix. Fractionation of the S9 mix made guinea pig S9 active and mouse S9 inactive. Diet is another factor that can influence enzyme levels and modify results. These factors can modify the response over about a 100-fold range. This becomes significant when the mutagenic potency range of the assay falls to about  $10^3$ . Furthermore, some potent mutagens are noncarcinogenic but some potent carcinogens are nonmutagenic in this system. (35 refs)

- 78-2032 **Carcinogenesis Induced by 7,12-Dimethylbenz(a)anthracene in C3H-Avylf Mice: Influence of Different Dietary Fats.** (Eng) Hopkins, G. J. (Dept. Biochemistry, Health Sciences Centre, Univ. Western Ontario, London, Ontario N6A 5C1, Canada); Hard, G. C.; West, C. E. *J Natl Cancer Inst* 60(4): 849-853; 1978.

The incidence and types of 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors were studied in C3H-Avylf mice fed a high-fat diet containing either polyunsaturated or saturated fat. After receiving one of these diets for 28 days, some mice were given an intragastric dose of 5 mg DMBA. To identify the stage of carcinogenesis that might be influenced by dietary fat, the diets of half the mice were then interchanged, so that those previously fed the saturated fat diet were fed the polyunsaturated fat diet and vice versa. The cumulative incidence of tumor-bearing mice was significantly greater among females fed the polyunsaturated fat diet, compared to those fed the saturated fat diet. This enhancement of carcinogenesis was observed only when the mice were fed the polyunsaturated fat diet after DMBA administration. Similar findings were obtained in male mice, but these mice developed fewer tumors and none of the differences were statistically significant. Male mice developed tumors of the liver, lungs, and skin; females developed tumors of the mammary glands and ovaries. It is suggested that the large amounts of linoleic acid in the polyunsaturated fat diet could have facilitated neoplastic proliferation. (21 refs)

- 78-2033 **Effects of Carcinogens or Suspected Carcinogens on Viral Leukemogenesis in C57BL/10, SJL/J Mice and Their F<sub>1</sub> Hybrid (Meeting Abstract).** (Eng) Raikow, R. B. (Allegheny General Hosp., Pittsburgh, PA, 15212). *Proc Am Assoc Cancer Res* 19: 23; 1978. (no refs)

- 78-2034 **Metabolism of Carcinogens to Mutagens by Mammary Tissue Extracts (Meeting Abstract).** (Eng) Maack, C. A. (G. W. Hooper Foundation, Univ. California, San Francisco, CA, 94143); White, T. J.; Lee, R. E.; Lyon, M.; Petrakis, N. L. *Proc Am Assoc Cancer Res* 19: 229; 1978. (no refs)

- 78-2035 **Reduction of Carcinogenicity for Mouse Skin of Cigarette Smoke Condensate with Palladium Catalyst (Meeting Abstract).** (Eng) Kensler, C. J. (Life Sciences, Arthur D. Little Inc., Cambridge, MA, 02140); Thayer, P. S.; Mold, J. D.; Bryant, H. G. *Proc Am Assoc Cancer Res* 19: 185; 1978. (no refs)

- 78-2036 **The Mutagenicity of Airborne Particulate Pollutants.** (Eng) Dehnen, W. (Medizinisches Institut für Lufthygiene und Silikoseforschung, Universität Düsseldorf, Gurlittstrasse 53, D-4000 Düsseldorf, W. Germany); Pitz, N.; Tomingas, R. *Cancer Lett* 4(1): 5-12; 1978.

The mutagenic effect of extracts derived from airborne particulate matter, collected at two sites in a highly industrial city (iron and steel production, coke production, and refinery and chemical industries), was investigated with the Ames test. In each of the three *Salmonella typhimurium* tester strains used, TA1537, TA1538, and TA98, the highest mutagenic activity was found in the whole extract. When the extract was split into several fractions, the fraction containing the polycyclic aromatic hydrocarbons (PAH) showed the lowest mutagenic rate that was enzymatically mediated. A portion of the whole extract and three of the four fractions were mutagenic without metabolic activation. These results indicate that the mutagenic activity of the extracts from particulate airborne matter is predominantly based on compounds other than PAH. (11 refs)

- 78-2037 **Rat Liver Induction by Representative Chlorinated Hydrocarbons as Determined by Bacterial Mutagenesis (Meeting Abstract).** (Eng) Schoeny, R. (Dept. Microbiology, Univ. Cincinnati Medical Center, Cincinnati, OH); Loper, J. C.; Smith, C. C. *Mutat Res* 53(1): 69; 1978. (no refs)

- 78-2038 **Lung Cancer Risk in Pipe and Cigar Smokers (Letter to Editor).** (Eng) Bohrer, S. P. (Univ. Rochester Medical Center, Rochester, NY). *Br Med J* 1(6109): 369; 1978.

In order to settle the controversy of whether pipe and cigar smokers have a reduced risk of lung cancer, the risk of the cancer should be determined in pipe and cigar smokers who do and do not inhale. Another reason for the study is the fact



many former cigarette smokers have taken up smoking and pipes, and these are the ones most likely to inhale smoke. (7 refs)

**39 Immunosuppression in the Mouse Induced by Long-Term Exposure to Cigarette Smoke.** (Eng) P. G. (Dept. Microbiology, Univ. Western Australia, Perth, 6009, W. Australia); Keast, D.; Mackenzie, J. S. *Pathol* 90(1): 281-284; 1978.

Immunosuppression in the mouse exposed to cigarette smoke is considered as a model for human infectious and chronic respiratory diseases associated with cigarette smoking. In mice exposed to their body-wt equivalent of 20 cigarettes/day, antibody production within the lung is depressed within 2 wk. In contrast, regional lymph node and systemic activity shows enhancement for up to 16 weeks following continuous exposure before eventual suppression. Similar changes in murine immunologic function are also following long-term exposure to industrial air pollution. Therefore, synergism between cigarette smoking and air pollution in the etiology of respiratory disease may be appreciable in immunologic terms. The data suggest that immunologic function in many may be affected by long-term exposure to cigarette smoke. Cigarette smokers exhibit elevated prevalence rates of infectious and neoplastic disease, particularly at sites associated with the respiratory tract. Under normal conditions, immunologic mechanisms operative in the respiratory tract are known to provide the major defense against infectious disease. Similar mechanisms may also operate against the development and spread of neoplasms. Data from this model suggest that cigarette smoke-induced immunosuppression may be involved in the etiology and pathogenesis of diseases associated with cigarette smoking. (27 refs)

**40 Isoniazid Tumorigenicity in Mice Under Different Experimental Conditions.** (Eng) Bhide, S. V. (Cancer Res. Inst. and Pathology Dept., Tata Memorial Hospital, Parel, Bombay 400012, India); Maru, G. B.; Sawai, S. I.; Ranadive, K. J. *Int J Cancer* 21(3): 381-386; 1978.

Tumorigenicity of isoniazid was studied in 11- or 12-wk-old Swiss mice fed doses of 0.55, 1.1, and 2.2 mg/mouse/day by gavage; the treatment was continued throughout the life-span of the animals. The highest dose was toxic, and only 3/30 mice survived 24 mo; 1/3 survivors developed lung adenocarcinoma. Another group of six mice was treated with 2.2 mg/day for only 4 mo, and all six developed lung tumors. A total of 16/29 mice fed 1.1 mg/day developed lung tumors by 24 mo, 15 of which were of the lung. At the lowest dose, 6 tumors (4 lung) were noted in 19 mice by 24 mo. Treatment of virgin and breeder Swiss mice with a dose of 2.2 mg/day resulted in tumors in 8/25 and 10/19 mice, respectively, by 24 mo. All tumors in the virgins and five of

those in the breeders were lung tumors. Treatment of mice with 0.55 or 1.1 mg/day from day five of gestation to 12 wk postpartum resulted in tumors in 7/14 and 8/9 mice, respectively, by 24 mo. None of the animals in the latter group survived beyond 18 mo; there were three lung tumors in the former group and six in the latter. In vitamin B complex-deficient mice fed 1.1 mg/day, the cumulative tumor incidence reached 12/21 (8 lung) by 24 mo. In protein-deficient mice fed 0.55 or 1.1 mg/day, the respective tumor incidences were 6/11 (3 lung) and 9/17 (7 lung) by 24 mo. Treatment of A strain mice with 1.1 or 2.2 mg/day resulted in tumors in 10/16 (7 lung) and 6/11 (6 lung) mice; by 24 mo all other tumors noted were hepatic. Thus, isoniazid produces lung and liver tumors in Swiss and A strain mice. (53 refs)

**78-2041 Reaction of Nicotine and Sodium Nitrite: Formation of Nitrosamines and Fragmentation of the Pyrrolidine Ring.** (Eng) Hecht, S. S. (Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Chen, C. B.; Orna, R. M.; Jacobs, E.; Adams, J. D.; Hoffmann, D. *J Org Chem* 43(1): 72-76; 1978.

The reaction of nicotine and sodium nitrite was investigated to provide insight on the formation of potentially carcinogenic tobacco-specific nitrosamines. Reaction at 20 C for 17 hr resulted in the formation of N'-nitroso-nornicotine (1), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (2), and 4-(N-methyl-N-nitrosamino)-4-(3-pyridyl)butanal (3) in yields of 0.1%-2.8%. Most of the nicotine (80%-90%) was unreacted under these mild conditions. When the reaction was carried out at 90 C with a fivefold excess of sodium nitrite, 75%-85% of the nicotine reacted, and nitrosamines 1 and 2 were formed in higher yield (up to 13.5% and 4.3%, respectively); nitrosamine 3 was not observed. Under these conditions, both 2 and 3 gave secondary products: 2 was nitrosated further to give 4-(N-methyl-N-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone and 3 gave rise to 1-methyl-5-(3-pyridyl)pyrazole. The major products resulting from fragmentation of the pyrrolidine ring were cis- and trans-3-(3-pyridyl)acrylonitrile, N-methylnicotinamide, and nicotinic acid. (31 refs.)

**78-2042 Sebaceous Gland Suppression Tests as an Indicator of the Carcinogenic Activity of Experimental Cigarette Smoke Condensates (CSC) (Meeting Abstract).** (Eng) Bock, F. G. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Gori, G. B. *Proc Am Assoc Cancer Res* 19: 43; 1978. (no refs)

**78-2043 Metabolism of the Tobacco Specific Carcinogen, N'-Nitroso-nornicotine (Meeting Abstract).**



(Eng) Chen, C. B. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Hecht, S. S.; Hoffmann, D. *Proc Am Assoc Cancer Res* 19: 116; 1978. (no refs)

**78-2044 Substitute-Tobacco Tar Toxicity (Letter to Editor).** (Eng) Busch, F. (Sch. Public Health, Univ. California, Berkeley, CA, 94720); Seid, D.; Wei, E. T. *Lancet* 1(8064): 614; 1978.

The mutagenic potential of tars from cigarettes with tobacco substitutes was assayed using *Salmonella typhimurium* strain TA 98. The tars from these cigarettes were at least as mutagenic as the tars from cigarettes without substitutes. (8 refs)

**78-2045 Lipid Distribution in Flue-cured Tobacco Plants.** (Eng) Ellington, J. J. (Tobacco Lab., Agricultural Res. Service, U.S. Dept. Agriculture, Athens, GA, 30604); Schlotzhauer, P. F.; Schepartz, A. I. *J Agric Food Chem* 26(2): 407-410; 1978.

Various tobacco plant parts of three varieties used in the manufacture of reconstituted tobacco sheet were analyzed for the polycyclic aromatic hydrocarbon precursors solanesol and neophytadiene, hydrocarbon waxes, total major fatty acids, and total sterols. Total lipid content was highest in the strip, followed by the whole leaf, stem, and stalk. Solanesol was present in the whole leaf and strip only; neophytadiene was found in strip and stem tissue only. (18 refs)

**78-2046 Oral Contraceptives, Smoking and Nodular Hyperplasia of the Liver.** (Eng) Lough, J. (Dept. Pathology, Montreal General Hosp., 1650 Cedar Ave., Montreal, PQ H3G 1A4, Canada); Kinch, R.; Spellman, S.; Shaffer, E. *Can Med Assoc J* 118(4): 403-404; 1978.

Case reports of four women with focal nodular hyperplasia of the liver are presented with emphasis on their oral contraceptive (OC) and smoking histories. The first was a 44-yr-old who had taken OC for 6 yr before admission and who smoked irregularly. The second was a 21-yr-old who had taken OC for 4 yr and had smoked at least a pack of cigarettes a day for 5 yr. The third was a 40-yr-old who had taken OC for 4 yr and had smoked 1.5 packs of cigarettes a day for many years. The last was a 45-yr-old who had taken OC for 6 yr before admission and had smoked 15-20 cigarettes a day. In each case, the sectioned surface of the liver was multinodular, with a central fibrous scar radiating into the parenchyma and resembling that of focal postnecrotic cirrhosis. Intimal proliferation of the vessels was marked, and fibrin thrombosis was seen occasionally. It is suggested that OC use and ciga-

rette smoking may have a synergistic effect on coagulation in susceptible women. (17 refs)

**78-2047 Metabolic Deactivation of Mutagens in the *Salmonella*-Microsome Test.** (Eng) De Flora, S. (Inst. Hygiene, Univ. Genoa, 16132 Genoa, Italy). *Nat* 271(5644): 455-456; 1978.

The possibility that the mutagenic potential of some compounds may be deactivated in the *Salmonella typhimurium* microsome assay was investigated. Sodium azide, sodium chromate, sodium nitrite, 5-nitro-2-furoic acid, captan, and 2-aminofluorene were tested for mutagenicity using *S. typhimurium* strain TA100. Assays were performed in the presence and absence of an S-9 liver microsomal fraction (10  $\mu$ l/plate) from Aroclor 1254-induced rats mixed with 0.5 of an NADPH-generating system. 2-Aminofluorene was mutagenic only after the S-9 mix was added. The other compounds were mutagenic without the S-9 mix, and its addition decreased the number of revertant colonies significantly. The loss of mutagenic activity was complete at low doses of test compounds; larger doses exceeded the deactivation capacity of the S-9 mix except for sodium dichromate, which was totally deactivated below the toxic concentration (80  $\mu$ g). Both deactivation and activation were related with the amounts of liver microsomal fraction embedded in soft agar; revertants were not affected significantly by the addition of S-9 cofactors with the microsomal fraction. (14 refs)

**78-2048 High Rate of Endoreduplications and Chromosomal Aberrations in Hamster Cells Treated with Sodium Nitrite In Vitro.** (Eng) Tsuda, H. (Dept. Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corp., Hatano, Kanagawa, 257, Japan); Kato, K. *Mutat Res* 56(1): 69-73; 1978.

Sodium nitrite ( $\text{NaNO}_2$ ) was examined for its potential to induce chromosomal damage in hamster cells in vitro. Syrian hamster embryo cells were exposed for 24 hr to  $\text{NaNO}_2$  at various concentrations and then maintained in a normal medium for another 24 hr. Colcemid was added during the last 3 hr. At 50 mM,  $\text{NaNO}_2$  induced a significant increase in the frequency of chromosomal aberrations, the main aberrations being single chromatid breaks and chromatid exchanges. At lower concentrations (20 and 30 mM), abnormal metaphases were observed at a four to seven times higher frequency than in nontreated cultures, with the predominant aberrations being chromatid gaps. In cells treated with 50 mM  $\text{NaNO}_2$ , > 10% of the metaphase cells were endoreduplicated with typically paired diplochromosomes. Chromosomal aberrations, including gaps, breaks, and exchanges, were also seen in diplochromosomes. It is suggested that nitrite



the ratio of -SH/-S-S- in nuclear proteins and disturb the mechanism of cell division in a manner similar to that of SH reagents, resulting in endoreduplication. (17 refs)

**78-2049 Carcinoma of the Esophagus of Rabbits Induced with N-Methylbenzylamine and Sodium Nitrite.** (Eng) Iizuka, T. (Serology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Ichimura, K.; Kawachi, T.; Hirota, T.; Itabashi, M. *Gann* 68(6): 829-835; 1977.

Esophageal carcinomas were induced in 3/5 New Zealand white rabbits given 0.25% N-methylbenzylamine and 0.16% sodium nitrite (NaNO<sub>2</sub>) in their drinking water. The three rabbits with carcinoma had consumed >94 g of NaNO<sub>2</sub> and survived >536 days. The carcinomas were slightly elevated, and no polypoid lesions were seen. Histologically, the tumors were squamous cell carcinomas or adenosquamous carcinomas. No metastases were found. (8 refs)

**78-2050 Effects of N-Nitrosodiethanolamine and 1,1-Diethanolhydrazine in Syrian Golden Hamsters.** (Eng) Hilfrich, J. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Schmeltz, I.; Hoffmann, D. *Cancer Lett* 4(1): 55-60; 1978.

The carcinogenicity of N-nitrosodiethanolamine (NDEA) and 1,1-diethanolhydrazine (DEH) was investigated in Syrian golden hamsters. The animals were divided into five groups and treated as follows: Group 1 received 7 sc injections of 2,260 mg NDEA/kg for a total dose of 15.8 g/kg; Group 2 received 27 sc injections of 565 mg NDEA/kg for a total dose of 15.3 g/kg; Group 3 received 78 sc injections of 14.0 mg DEH/kg for a total dose of 1.1 g/kg; Group 4 received 78 sc injections of 3.5 mg DEH/kg for a total dose of 273 mg/kg; Group 5 received 78 sc injections of saline. In Group 1, tumors were noted in 12/15 males and 8/15 females; in Group 2, the respective figures were 8/15 and 1/15. The most common neoplasms in these groups were poorly differentiated adenocarcinomas of the nasal cavity and noninfiltrating papillary tumors of the trachea. The first nasal tumor was noted 35 wk after treatment in Group 1, and the first tracheal tumor appeared 46 wk after treatment in Group 1. Furthermore, three hepatocellular adenomas (Group 1) and three injection site fibrosarcomas (Group 2) were noted. The tumors appearing in Groups 3 and 4 corresponded to expected spontaneous neoplasms, with the possible exception of two malignant lymphomas that occurred in Group 3. Thus, NDEA is carcinogenic in the Syrian hamster and DEH is not. (17 refs)

**78-2051 Atmospheric Nitrosamines.** (Rus) Bretshneider, K. (Dept. Communal Hygiene, Humboldt

Univ., Berlin, E. Germany); Horn, K.; Matz, J. *Gig Sanit* (7): 86-87; 1977.

A relatively simple and accurate chromatographic assay for the detection of atmospheric nitrosamines (NA) is described. NA concentration was found to be correlated with the incidence of various pathologic symptoms in workers occupationally exposed to these compounds. (no refs)

**78-2052 Carcinogenic Effects of Nitrosamines That May Be Formed in Water-soluble Cutting Liquids.** (Ger) Schuster, D. (Am Kaferberg 7, D-6741 Frankweiler, W. Germany). *Seifen Ole Fette Wachse* 103(18): 529-530; 1977.

Cooling and cutting liquids used in the metal-working industry contain nitrites and amines. The nitrites should be replaced by nontoxic substances to prevent the formation of carcinogenic nitrosamines in these liquids. (no refs.)

**78-2053 Studies on [<sup>3</sup>H] Thymidine Incorporation into Rat Esophageal DNA (TI): Enhancement by *Bidens Pilosa* (BDP), A South African Vegetable (Meeting Abstract).** (Eng) Mirvish, S. S. (Eppley Inst. Cancer Res., Univ. Nebraska Medical Center, Omaha, NB); Rose, E. F. *Proc Am Assoc Cancer Res* 19: 163; 1978. (1 ref)

**78-2054 Effect of Iodoacetamide or Tween 60 on Methylnitrosocyanamide Carcinogenesis in Rat Glandular and Forestomach.** (Eng) Fukushima, S. (Dept. Pathology, Sch. Medical Technology and Nursing, Nagoya Hoken-Eisei Univ., 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi-ken 470-11, Japan); Hibino, T.; Shibata, M.; Tsuda, H.; Shirai, T.; Takahashi, M.; Ito, N. *Gann* 68(6): 813-818; 1977.

The effect of iodoacetamide or Tween 60 on the carcinogenicity of methylnitrosocyanamide (MNC: 25 mg/liter drinking water for 28 wk) was examined in Wistar rats. The incidence (78.3%) of forestomach papillomas and squamous cell carcinomas increased significantly in rats given 0.01%-0.1% iodoacetamide during the first 10 wk of MNC administration. Of the 22 rats treated simultaneously with 0.4% Tween 60 and MNC for 28 wk, 2 developed tumors of the glandular stomach. Histologically, one of these was a well-differentiated adenocarcinoma and the other was polypoid hyperplasia. The results indicate that under certain conditions, MNC is carcinogenic for the rat glandular stomach in addition to the forestomach. Tween 60 might act by facilitating direct contact between MNC and the glandular stomach mucosa. (21 refs)



- 78-2055 Carcinogenicity of 1-Oxopropylpropylnitrosamine (N-Nitroso-N-propyl-propionamide) in Syrian Hamsters.** (Eng) Althoff, J. (Eppley Inst. Res. in Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105); Grandjean, C.; Gold, B.; Runge, R. *Z Krebsforsch* 90(3): 221-225; 1977.

The carcinogenicity of 1-oxopropylpropylnitrosamine (1-OPPN) was investigated in Syrian hamsters. The LD50 was determined by a single sc treatment of 125, 250, 500, or 1,000 mg/kg. In chronic studies, the hamsters received sc doses of 30, 15, or 7.5 mg/kg. The LD50 was 354 mg/kg for females and 268 mg/kg for males. In the chronic studies, av survival, tumor latency, and incidence showed a positive dose-response relationship. The main target was the sc tissue, where tumors could be palpated 20 wk after the beginning of treatment. Most of the neoplasms were sarcomas of varying differentiation. The tumors were locally invasive and showed local and distant metastases to the lymph nodes, lungs, kidneys, and liver. 1-OPPN also had a systemic effect, with tumors developing in the nasal cavity, larynx, trachea, lungs, forestomach, and vagina. (12 refs)

- 78-2056 Pattern of Lung Cancer Induction by Oral Administration of N-Bis(2-Hydroxypropyl) Nitrosamine (DHPN) in Rats (Meeting Abstract).** (Eng) Konishi, Y. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., Nara, Japan); Kondo, H.; Ikeda, T.; Kawabata, A.; Shoji, Y.; Inui, S. *Proc Am Assoc Cancer Res* 19: 95; 1978. (no refs)

- 78-2057 Assessment of Dipropylnitrosamine Levels in a Tomato Field Following Application of Treflan EC.** (Eng) Ross, R. (Thermo Electron Res. Center, Waltham, MA, 02154); Morrison, J.; Fine, D. H. *J Agric Food Chem* 26(2): 455-457; 1978.

A tomato field was sprayed with a herbicide containing N-nitrosodipropylamine (NDPA) as an impurity, and air, soil, irrigation water, and crop samples were obtained and analyzed for NDPA contamination. No NDPA residues were detected. Max exposure due to inhalation or to the ingestion of contaminated drinking water or the tomatoes has been found to be less than the estimated levels of general human nitrosamine exposure. Volatilization is suggested to be the major route of environmental dissipation. (19 refs)

- 78-2058 Islet Cells as a Component of Pancreatic Ductal Neoplasms. I. Experimental Study: Ductular Cells, Including Islet Cell Precursors, as Primary Precursor Cells of Tumors.** (Eng) Pour, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd

and Dewey Ave., Omaha, NB, 68105). *Am J Pathol* 90(2): 295-316; 1978

The primary target cells for N-nitrosobis(2-oxopropyl)amine (BOP) carcinogenesis in the pancreas were investigated in Syrian hamsters. Animals were given weekly sc BOP injections (10 mg/kg) for 1-9 wk or single injections of 20 or 100 mg/kg and killed at intervals thereafter. Histologic examination of the pancreas indicated that ductular cells, especially those of periinsular and intrainsular origin, are the most responsive to the carcinogen. The neoplastic process was initiated by hyperplasia of the intercalated (intralobular) ductular and interlobular ductal cells. In many cases, the latter were associated with newly formed islets (nesidioblastosis). This process was followed by the excess formation of mature and, especially, immature islet cells and their precursors (IP) in the islet periphery and by the appearance, distention, and multiplication of periinsular and, particularly, intrainsular ductules. The concomitant proliferation of periinsular and intrainsular ductular cells and IP indicates a definite histogenetic relationship between these cells. These findings support the view that ductular cells (including IP) retain a reserve embryonic tissue potency during their life-span and mediate against an ectodermal derivation of the islet cell. The primary proliferation of intrainsular and periinsular ductules may be due to their longer contact with a blood-borne carcinogen or its metabolites through the extensive vessels of the islets or it may be related to the enzymatic patterns of these cells involved in carcinogen metabolism. (47 refs)

- 78-2059 The Effect of 1-Methoxypropylpropylnitrosamine in Syrian Golden Hamsters.** (Eng) Althoff, J. (Eppley Inst. Res. in Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105); Grandjean, C.; Gold, B. *Z Krebsforsch* 90(2): 215-219; 1977.

The carcinogenicity of 1-methoxypropylpropylnitrosamine (1-MPPN) was investigated in Syrian hamsters and compared with that of  $\alpha$ -dipropylnitrosamine (DPN) and acetoxypylpropylnitrosamine (1-APPN) using equitoxic doses and an sc route of administration. Acute toxicity experiments revealed an LD50 of 583 mg/kg for DPN, 458 mg/kg for females and 707 mg/kg for males for MPPN. In chronic experiments, doses of 60, 30, and 15 mg/kg were given sc once weekly for life to 30, 35, and 40 animals, respectively. Tumor incidence in the highest dose group was 90%: lung (90%), tracheal (78%), forestomach (48%), and nasal cavity (33%) tumors were found. Tumor incidence in the other dose groups was 100%. With 30 mg/kg, 100% developed lung, 86% tracheal, 43% forestomach, and 40% nasal cavity tumors. With 15 mg/kg, 100% developed lung, 70% tracheal, 53% forestomach, and 47% nasal cavity tumors. Contrary to 1-APPN, there were no tumors at the injection site, but 1-MPPN induced tumors of the upper digestive and re-



ory tract. The main target organ for DPN was lungs, but the pharynx and forestomach were not tested. (16 refs)

060 **Mutagenicity of Alkyl-( $\omega$ -hydroxyalkyl)-nitrosamines Related to Dibutylnitrosamine.** Olajos, E. J. (Dept. Environmental and Industrial Chem., Sch. Public Health, Univ. Michigan, Ann Arbor, MI); Maverakis, N.; Cornish, H. H. *Mutat Res* 56(3): 223; 1978.

us alkyl-( $\omega$ -hydroxyalkyl) derivatives related to dibutylnitrosamine (DBN) were tested for mutagenicity to *Salmonella typhimurium* in the absence of a liver microsomal activation system. Butyl-(4-hydroxybutyl)nitrosamine, butyl-(2-hydroxypropyl)nitrosamine, and butyl-(2-hydroxyethyl)nitrosamine were all mutagenic to *S. typhimurium* strain TA1535 in the absence of an activation system. There was a simple dose-response relationship, and no significant differences in the mutagenicity of the compounds occurred as the alkyl side chain possessing the OH group increased in length. It is suggested that mutagenesis of *S. typhimurium* by the higher dialkyl nitrosamines is partly due to the formation of  $\omega$ -hydroxylated derivatives in addition to the major mutagenic metabolite derived from  $\alpha$ -dealkylation. (22 refs)

061 **Induction of Transitional Cell Carcinomas (TCC) with N-Butyl-(4-hydroxybutyl)nitrosamine (OH-BBN) in Female Rats** (Meeting Abstract). (Eng) Becci, P. J. (IIT Res. Inst., Chicago, IL); Grubbs, C. J.; Moon, R. C.; Sporn, M. B. *Proc Soc Exp Biol Med* 19: 73; 1978. (no refs)

062 **Carcinogenesis in Heterotopic Urinary Bladders (HUB) (Meeting Abstract).** (Eng) Sugihara, N. (Medical Coll. Pennsylvania, Philadelphia, PA, 19129); Leighton, J.; Zajac, B.; Troll, W.; Belman, S. *Proc Soc Exp Biol Med* 19: 36; 1978. (no refs)

063 **Damage and Repair of DNA in Urinary Bladder Epithelium of Rats Treated with N-Butyl-N-(4-hydroxybutyl)nitrosamine.** (Eng) Tsuda, H. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Showa-cho, Mizuho-ku, Nagoya 467, Japan); Miyata, Y.; Hara, A.; Hasegawa, R.; Shirai, T.; Ito, N. *Gann* 68(6): 83; 1977.

yl-N-(4-hydroxybutyl)nitrosamine (BBN), which se-

lectively induces urinary bladder tumors in several animal species, was found to cause DNA damage in the rat bladder epithelium. Wistar rats were given 100 mg/kg BBN iv and killed after 2, 6, 12, 24, or 48 hr. DNA damage was examined by measuring the change in sedimentation pattern in an alkaline sucrose gradient. The amount of DNA in each fraction was determined by fluorescence spectrophotometry. At 2 hr, the sedimentation profile shifted from heavier (No. 15, control peak) to lighter (Nos. 2-4) fractions, and the max effect appeared at 6 hr as a single peak in the lighter fractions. At 12 hr, two peaks of DNA repair were present, one light and one heavy. At 48 hr, the sedimentation profile showed a single peak identical with that of controls, indicating complete repair of DNA. (12 refs)

78-2064 **Genetic Variations in the Induction of Bladder Tumors.** (Eng) Diwan, B. A. (Meloy Labs., Inc., Springfield, VA, 22151); Fox, A.; Blackman, K. E. *Naturwissenschaften* 64(12): 647-649; 1977.

Genetic variations in the induction of bladder tumors were studied in AKR/J, BALB/cJ, and C57BL/KSJ mice given dibutyl nitrosamine (DBN: 200 mg/kg/wk sc for 10 wk). Of 12 female C57BL/KSJ mice, 5 had transitional cell carcinoma (TCC) of the bladder and 2 had leukemia; of 13 males, 6 had TCC, 1 had squamous cell carcinoma (SCC) of the bladder and 2 had leukemia. Of 11 BALB/cJ females, 2 had TCC, 1 SCC, and 3 leukemia; of 14 males, 5 had TCC and 2 had leukemia. AKR/J mice developed leukemia only: 11/13 females and 11/12 males. The absence of bladder tumors in these mice could be due to the fact that they died from leukemia before tumors could develop or that the AKR leukemia virus interfered with or inhibited tumor development. Hepatomas were associated with DBN treatment in BALB/cJ and C57BL/KSJ mice; SCC of the nasal cavity was also associated with the treatment in the latter group. (6 refs.)

78-2065 **Mode of Mutagenic Action of 4-Benzoylamido- and 4-Acetamido-4-carboxamido-n(N-nitroso)-butylcyanamide.** (Eng) Otsuji, N. (Dept. Microbiology, Faculty Pharmaceutical Sciences and Cancer Res., Kyushu Univ., Fukuoka, Japan); Endo, H. *Mutat Res* 49(1): 9-18; 1978.

The mode of mutagenic action of 4-benzoylamido- and 4-acetamido-4-carboxamido-n(N-nitroso) butylcyanamide (BCNBC, ACNBC) was studied in several strains of *Escherichia coli* K12. Strains carrying defects in the DNA repair mechanism, AB2463 (*recA*) and P3478 (*polA*), were more sensitive than their parent strains to both compounds, but AB1886 (*uvrA*) showed the same sensitivity as the parent strain. Mutations were then induced in BE1043 [*trp(amb)*-



*pho(amb)*] by exposing them to varying concentrations of BCNBC and ACNBC. Approx 90% of the tryptophan revertants were due to mutations in suppressor genes. Suppressor analysis using BE1047 [*trp(amb)pho(och)*] indicated that the most frequently occurring reversion was due to a mutation in the suppressor gene *supE*. These findings suggest that the two alkyl nitrosocyanamides predominantly induce guanine:cytosine--adenine:thymine transition. (29 refs)

**78-2066 Enhancing Effect of Harman on Mutagenicity in Salmonella.** (Eng) Matsumoto, T. (Central Res. Inst., Japan Tobacco and Salt Public Corp., 6-2 Umeoka, Midoriku, Yokohama, Kanagawa 227, Japan); Yoshida, D.; Mizusaki, S. *Mutat Res* 56(1): 85-88; 1977.

When the nonmutagenic portions of a tryptophan pyrolyzate were added to the mutagenic portions, the mutagenicity of the latter was increased markedly. Upon purification, the inactive fractions were found to contain large quantities of harman and indole derivatives. In further experiments, harman, indole, and skatole increased the mutagenicity of eight known mutagens, but none of the three compounds alone had any effect. The mechanism of this enhancement is unknown. (9 refs)

**78-2067 Dietary Effects on the Pharmacokinetics of Three Carcinogenic Nitrosamines.** (Eng) Wishnok, J. S. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Rogers, A. E.; Sanchez, O.; Archer, M. C. *Toxicol Appl Pharmacol* 43(2): 391-398; 1978.

The concentrations of N-nitrosodimethylamine (DMN), N-nitrosodiethylamine (DEN), and N-nitrosodibutylamine (DBN) were monitored as a function of time in the blood and liver of rats fed either a normal diet (1) or a diet marginally deficient in lipotropes (2) for 3 wk. Undiluted DBN was injected ip at a dose of 100 mg/kg; DMN and DEN were diluted and given ip at 3 and 25 mg/kg, respectively. Rats were killed at intervals from 15 to 210 min after DMN or DEN administration and from 15 to 480 min after DBN. The disappearance of each nitrosamine from the blood showed first-order kinetics. The hepatic clearance of DEN and DBN was also first-order, but the hepatic clearance of DMN could not be described by a simple rate expression. The clearance of DEN and DMN from the blood was decreased in rats fed diet 2. The hepatic clearance of DEN was not affected by diet. In contrast, the clearance of DEN from both blood and liver was increased at least twofold in rats fed diet 2. With DMN, the time dependence of its concentration in liver tissue showed anomalous behavior with both diets. Of the three nitrosamines, only DMN has been found to be insensitive toward diet in its carcinogenic effect. Thus, diet-related dif-

ferences in the pharmacokinetic data do not explain the previously reported variations in the carcinogenicity of DEN and DBN due to diet. (17 refs)

**78-2068 Activation of N-Nitrosamines to Alkylating Agents by Rat Liver Nuclei and Microsomes Binding to Endogenous and Exogenous DNA (Meeting Abstract).** (Eng) Grandjean, C. J. (Eppley Inst. Res. Cancer, Omaha, NB, 68105); Gold, B. I.; Knepper, S.; Morris, J. *Proc Am Assoc Cancer Res* 19: 185; 1978. (no refs)

**78-2069 Enzymatic Removal In Vitro of Methylguanine from DNA Alkylated by Administration of Dimethylnitrosamine (Meeting Abstract).** (Eng) Pegg, A. E. (Dept. Physiology, Milton S. Eisenhower Medical Sch., Pennsylvania State Univ., Hershey, PA 17033); Hui, G. *Proc Am Assoc Cancer Res* 19: 60; 1978. (no refs)

**78-2070 Comparison of In Vitro Tests in Syrian Hamster Cells for Detection of Carcinogens (Meeting Abstract).** (Eng) Casto, B. C. (BioLabs, Inc., Northbrook, IL 60062); Janosko, N.; Meyers, J.; DiPaolo, J. A. *Proc Am Assoc Cancer Res* 19: 83; 1978. (no refs)

**78-2071 De Novo Replication and Repair Replication of DNA During Diethylnitrosamine-induced Carcinogenesis.** (Eng) Craddock, V. M. (MRC Toxicology Unit, Woodmansterne Road, Carshalton, Surrey, England); Henderson, A. R. *Cancer Lett* 3(5/6): 277-284; 1977.

An attempt was made to determine whether stimulation of de novo replication or inhibition of repair replication is a relevant event underlying the minimum feeding period in diethylnitrosamine (DEN)-induced carcinogenesis. Female star rats were fed a diet containing 90 ppm DEN, and de novo DNA synthesis was measured at 3, 6, 9, and 12 wk. The diet increased the number of replicating diploid and tetraploid nuclei, with a max occurring at 6 wk. After 3 wk of feeding, the stimulation of tetraploid nuclei was less than that of diploid nuclei, but by 9 wk, the ratio of replicating tetraploid to replicating diploids was normal. The effect of the diet on the capacity of the cell for repair replication was studied using hydroxyurea (HU) to inhibit de novo replication. In rats fed the diet for 8 wk, an injection of HU began at the same time as, and 30 min after an injection of <sup>3</sup>H-thymidine reduced de novo replication to a low level, and no repair replication was noted. F



ver, when animals were inoculated with 20 mg/kg methylnitrosamine 2 hr prior to <sup>3</sup>H-thymidine injection, with the same HU treatment, repair replication took place in animals on the diet for 8 wk. These findings indicate that a critical minimum time of DEN feeding is necessary for the development of restorative hyperplasia, when the increased rate of DNA replication increases the probability of DNA synthesis taking place before the carcinogen-induced damage has been repaired. (13 refs)

78-2072 **Liver Cell-mediated Mutagenesis of Mammalian Cells with Hepatocarcinogens (Meeting Abstract).** (Eng) Langenbach, R. (Eppler Inst. Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NB); Freed, H. J.; Luberman, E. *Proc Am Assoc Cancer Res* 19: 62; 1978. (no refs)

78-2073 **Activity and Isozyme Spectrum of Hexokinase and Pyruvate Kinase in Liver Carcinogenesis and Primary Hepatomas.** (Rus) Kildema, L. A. (Inst. Experimental and Clinical Medicine, Tallin, USSR). *Vestn Akad Med Nauk SSSR* (1): 68-71; 1978.

The activity and isozyme spectra of two key hepatic glycolysis enzymes, hexokinase (HK) and pyruvate kinase (PK), were studied in Wistar rats with diethylnitrosamine (DEN: 2.5 mg/kg po, 6x/wk for 8 mo)-induced hepatomas. Both HK and PK activity increased gradually during hepatocarcinogenesis, and by the end of the experiment (8 - 10 mo), the activity in the tumor tissue was approx 1.5 - 2 times greater than that in normal liver. Chromatographic assay of the enzyme spectra showed a slight increase in the first three HK isozymes and a decrease in the content of L-type PK. (11 refs.)

78-2074 **Metabolism of N-Nitrosamines in Cultured Human Colon (Meeting Abstract).** (Eng) Autrup, H. (Human Tissue Studies Section, Experimental Pathology Branch, NCI, Bethesda, MD, 20014); Trump, B. F.; Harris, C. C. *Proc Am Assoc Cancer Res* 19: 14; 1978. (no refs)

78-2075 **Architecture and Ultrastructure of Carcinogen Induced Putative Preneoplastic Hepatocytes During Liver Carcinogenesis (Meeting Abstract).** (Eng) Ogawa, K. (Univ. Toronto, Toronto, Canada); Medline, A. *Proc Am Assoc Cancer Res* 19: 63; 1978. (no refs)

78-2076 **Spin-Trapping Demonstration of Hydroxyl Free Radical and Nitrosoamine Free Radicals Produced Upon Interaction of Carcinogens with Rat Liver Microsomes and Nuclei (Meeting Abstract).** (Eng) Floyd, R. A. (Oklahoma Medical Res. Foundation, Oklahoma City, OK, 73104). *Proc Am Assoc Cancer Res* 19: 166; 1978. (no refs)

78-2077 **Role of Hyperplasia in Hepatocarcinogenesis.** (Rus) Pyldvere, E. I. (Inst. Experimental and Clinical Medicine, Tallin, USSR). *Vestn Akad Med Nauk SSSR* (2): 75-77; 1978.

The role of hyperplasia in hepatocarcinogenesis was studied in C3HA mice and Wistar rats. The animals were divided into four groups: Group 1 included mice and rats who received diethylnitrosamine (2.5 mg/kg) in their drinking water; Group 2 included mice who received applications of o-aminoazotoluene (2x/wk); Group 3 included mice with spontaneous hepatocellular carcinomas; and Group 4 included the offspring of Group 2 mice. Oval cell proliferation, megalocytosis, and formation of complex biliary ducts were recorded only in Group 1; severe carbohydrate dystrophy without degenerative alterations was observed in both Groups 1 and 2. In Groups 3 and 4, the only features besides hepatocellular tumors were hyperplastic alterations. These findings indicate that diffuse hyperplasia is an initial stage of hepatocarcinogenesis. (13 refs.)

78-2078 **Carcinogen-induced Mallory Bodies in Liver Cells Studied In Vitro (Meeting Abstract).** (Eng) Borenfreund, E. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Higgins, P. J.; Peterson, E. *Proc Am Assoc Cancer Res* 19: 19; 1978. (1 ref)

78-2079 **Occurrence of Volatile N-Nitrosamines in Animal Diets.** (Eng) Kann, J. (Deutsches Krebsforschungszentrum Heidelberg, Institut für Toxikologie und Chemotherapie, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Spiegelhalter, B.; Eisenbrand, G.; Preussmann, R. *Z Krebsforsch* 90(3): 321-323; 1977.

A total of 46 samples of commercially available animal diets were analyzed for the presence of volatile N-nitrosamines. N-Nitrosodimethylamine was found in concentrations > 1 ppb in 80% of all samples, the highest value being 79 ppb. N-Nitrosopyrrolidine was detected in 59% of the samples, and 26 ppb was the max value. Three samples of one product showed trace quantities of N-nitrosodiethylamine, and 4 ppb N-nitrosopiperidine were found in one sample. Samples of the same diet from the same producer showed large differences



in nitrosamine content between different batches. Preliminary investigations indicate that fish meal is the main source of the contamination. (6 refs)

- 78-2080 Estimate of the Volatile Nitrosamine Content of UK Food.** (Eng) Gough, T. A. (Lab. Government Chemist, Stamford St., London SE1, England); Webb, K. S.; Coleman, R. F. *Nature* 272(5649): 161-163; 1978.

The volatile nitrosamine content of various foods commonly consumed in the United Kingdom was investigated using mass spectrometry and chemiluminescence. Each food sample was assayed for N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodi-n-propylamine, N-nitrosodi-n-butylamine, N-nitrosopiperidine, and N-nitrosopyrrolidine. Of 493 samples analyzed, cured meats represented the major source of volatile nitrosamines (av concentration 1.0  $\mu\text{g/kg}$ ) followed by fish (0.2  $\mu\text{g/kg}$ ) and cheese (0.4  $\mu\text{g/kg}$ ); all other foods contained an av of  $\leq 0.06$   $\mu\text{g/kg}$ . Based on these findings, it is estimated that the per person dialkyl nitrosamine intake in the normal diet is approx 1  $\mu\text{g/wk}$  and that of volatile heterocyclic nitrosamines is approx 3  $\mu\text{g/wk}$ . (13 refs)

- 78-2081 Opsonic Activity of Guinea Pig Serum is Reduced by In Vivo Administration of Carcinogenic Nitrosamines.** (Eng) Marom, Z. (Ina Sue Perlmutter Cystic Fibrosis Res. Center, Children's Hosp. Medical Center, Boston, MA, 02115); Brade, V.; Colten, H. R. *J Immunol* 120(3): 983-985; 1978.

N-Nitrosodiethylamine (DEN), N-nitrosodimethylamine (DMN), N-nitrosodibutylamine (DBN), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were injected im (10 mg/kg in 0.5 ml) into Hartley guinea pigs, and the effects of these carcinogens on the opsonic and phagocytic activity of the serum and macrophages, respectively, were determined. Peritoneal exudate (PE) cells and serum were harvested 3 days after the injection, and PE cells were induced with starch soln. For the phagocytic assay, batches of paraffin oil red O (ORO) *Escherichia coli* endotoxin emulsions were opsonized with serum from control or experimental animals. PE cells from animals given each of the nitrosamines were equally effective in ingesting ORO endotoxin-coated particles that were opsonized with normal guinea pig serum. In contrast, the serum from the treated animals failed to opsonize the particles for ingestion by either normal cells or those obtained from treated animals. The molecular basis of the nitrosamine-induced defect in opsonization is not known. However, neither a decrease in serum C3 nor factor B accounted for the marked reduction in this activity. DEN administration did decrease the levels of one heat-stable component required for opsonization; this component may be factor D. The results indicate that carcinogens may interfere with normal host de-

fenses before or coincident with tumor appearance. This effect may be critical in promoting tumor growth in the interval shortly after malignant transformation. (15 refs)

- 78-2082 Cinemicrographic Determination of Cell Progression and Division Abnormalities After Treatment with 1,3 Bis(2-Chloroethyl)-1-nitrosourea (BCNU) (Meeting Abstract).** (Eng) Ehmann, U. K. (Stanford Univ. Medical Center, Stanford, CA, 94305); Wheeler, K. *Proc Am Assoc Cancer Res* 19: 18; 1978. (no refs)

- 78-2083 An Adaptation of Alkaline Elution for Determining In Vivo Without Prelabeling DNA Damage from Chemical Carcinogens (Meeting Abstract).** (Eng) Pardi, S. (Dept. Oncology, Univ. Genoa, I-16132, Genoa, Italy); Taninger, M.; Bolognes, C.; Picca, M.; Brambilla, G. *Proc Am Assoc Cancer Res* 19: 128; 1978. (1 ref)

- 78-2084 Effect of Chlorpropamide on DNA Repair Replication in Chinese Hamster Ovary Cells (Meeting Abstract).** (Eng) Brown, R. F. (Southwest Texas State Univ., San Marcos, TX, 78666). *Fed Proc* 37(3): 23; 1978. (no refs)

- 78-2085 Nitrosoureas: Interaction with Chromatin and Effect on Poly (ADP-Ribose) Polymerase Activity at the Nucleosome Level (Meeting Abstract).** (Eng) Sudhakar, S. (Vincent T. Lombardi Cancer Res. Center, Georgetown Univ. Sch. Medicine, Washington, DC, 20007); Smulson, M. E. *Proc Am Assoc Cancer Res* 19: 123; 1978. (no refs)

- 78-2086 Modulation of Carcinogen-DNA Interaction by Polyamines (Meeting Abstract).** (Eng) Rajalakshmi, S. (Dept. Pathology, Univ. Toronto, Toronto, Canada); Sarma, D. S. *Proc Am Assoc Cancer Res* 19: 213; 1978. (no refs)

- 78-2087 Surgical Models of Carcinogenesis in Rat Large Bowel (Meeting Abstract).** (Eng) Kapnick, S. (Cancer Res. Inst., New England Deacon Hosp., Boston, MA, 02215); Monaco, A. P.; Balogh, K. *Proc Am Assoc Cancer Res* 19: 152; 1978. (no refs)



088 The Effects of Iodine Deficiency and Nutritional Supplementation on Hormone Dependent Mammary Cancer (Meeting Abstract). (Eng) Cave, W. T.; v. Rochester, Rochester, NY, 14642; Dunn, J. T.; Leod, R. *Proc Am Assoc Cancer Res* 19: 162; 1978. (no

089 Retinal Atrophy, Cataract, and Neoplasms in Wistar Rats After an Injection of N-Methyl-N-nitrosourea (MNU) (Meeting Abstract). (Eng) Murthy, A. Mason Res. Inst., Worcester, MA, 01508; Vawter, G. F.; rsen, R. A. *Proc Am Assoc Cancer Res* 19: 20; 1978. (1

090 Continual Requirement of Retinoid for Maintenance of Mammary Cancer Inhibition (Meeting Abstract). (Eng) Thompson, H. J. (IIT Res. Inst., Chicago, 0616); Grubbs, C. J.; Moon, R. C.; Sporn, M. B. *Proc Assoc Cancer Res* 19: 74; 1978. (no refs)

091 Experimental Induction of Melanotic Tumors in Syrian Golden Hamsters by Transplacental and Local Application of Ethylnitrosourea. (Eng) Pelfrene, A. MARLE, Sophia Antipolis, F-06560 Valbonne, France); L. A. *Z Krebsforsch* 90(3): 233-239; 1977.

nant Syrian golden hamsters were treated with a single ml/kg ip injection of a 1% soln of 1-ethyl-1-nitrosourea (U) a few hours before parturition. Offspring either received no further treatment or, from 6 wk of age, biweekly injection of ENU soln in acetone for 20 wk (total ENU, 13.4 mg per animal). Offspring from untreated mothers were also treated topically. Among all treated groups, 8.6% of the animals developed pigmented skin tumors, most of which animals having received the combined treatment. There was only a 0.5% incidence of spontaneous melanotic tumors in control animals. In the group receiving the combined treatment, the latency period was significantly decreased in females compared to males, but the total number of melanotic tumors induced was similar (15.6% and 14.8%, respectively). Most of the skin tumors, which were histologically and clinically benign, was transplanted several times, and it subsequently exhibited malignant features. (21 refs)

092 Oncogenic Properties of Transplacentally Acting Ethylnitrosourea in NMRI-Mice after Anterior X-Irradiation. (Eng) Schmahl, W. (Abteilung Nukleologie, Gesellschaft für Strahlen- und

Umweltforschung mbH, Munchen, D-8042 Neuherberg, W. Germany); Kriegel, H. *Z Krebsforsch* 91(1): 69-79; 1978.

The combined effects of prenatal x-irradiation (100 rads on days 11, 12, and 13 postconception) and ip ethylnitrosourea (ENU; 0.5 millimole/kg on day 17 postconception) were studied in NMRI mice. Pregnant mice received either x-rays alone (Group 1), ENU alone (Group 2), or both (Group 3). Although the development of the fetuses from both Groups 1 and 3 animals was greatly retarded with respect to Group 2 (1.33 g) and controls (1.31 g), there was still a significant difference between the wt of Group 1 (0.73 g) and Group 3 (0.58 g). The number of animals/litter was reduced in Group 3. A study of the dead or moribund animals between weaning and 18 mo of age revealed three leukemias each in Group 2 and 3, one fibrosarcoma in Group 2, and mild atrophy of the splenic white and red pulp associated with dilated sinusoids and small subcapsular hemorrhages in Groups 2 and 3. All surviving animals were sacrificed at 18 mo of age. Tumor incidence was 33.9% in Group 1, 27.6% in Group 2, and 38.0% in Group 3. Tumor multiplicity was approx 1.0 in the first two groups and 1.5 in the third. Group 3 had the highest incidence of leukemia, pancreatic adenomas, kidney cysts, and ovarian tumors. Group 2 had the highest incidence of lung tumors, liver tumors, ovarian cysts, and polyposis uteri. No nervous system tumors were noted in any treatment groups. Since the highest tumor incidences were noted in Groups 1 and 3, it is concluded that tumor occurrence in the offspring of x-irradiated animals cannot be altered significantly by ENU treatment. (29 refs)

78-2093 Carcinogenic Activity of Benzylnitrosourea (BNU) in BD Rats. (Ger) Ivankovic, S. (Institut für Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany). *Z Krebsforsch* 91(1): 63-68; 1978.

The carcinogenicity of N-benzyl-N-nitrosourea (BNU: po and sc LD<sub>50</sub> 550 mg/kg) was studied in male and female BD rats following chronic po and sc administration in oil. Twenty-seven 3-mo-old rats received BNU po (20 mg/kg, 3x/wk, total dose 1.6 g/kg, through gastric tube). All animals died from tumors, mainly squamous cell carcinoma of the forestomach. The av tumor induction time was 650 days. Metastases were found in four animals. Two animals also developed multicentric squamous cell carcinomas of the skin, two had ovarian tumors (granulosa cell tumor and clear cell carcinoma), and one rat developed myelogenous leukemia after 764 days. Twenty-five rats received BNU sc (20 mg/kg/wk, total dose 1.2 g/kg). Sixteen animals were evaluable; 13 of them developed sc tumors (mostly rhabdomyosarcomas) at the injection site. The av tumor induction time was 465 days. Fibrosarcoma was seen in two cases only, and one rat developed lymphocytic leukemia after 572 days. Two animals died tumor-free. No malignant tumors were found in control animals treated with the vehicle alone po or sc. Six pregnant rats



received a single dose of 125 mg/kg on the 20th day post-coitum. The mothers and their offspring were observed for about 800 and 760 days, respectively, during which time no malignant tumors were found. The findings indicate that BNU has a local carcinogenic effect following long-term administration and that the benzyl cation, as an alkylating agent, plays an important role in the carcinogenicity of BNU. (7 refs)

**78-2094 Tumorigenesis and Cytokinetics of Hamster Tracheal Epithelium After Exposure to N-Methyl-N-nitrosourea (MNU) (Meeting Abstract).** (Eng) Paradise, L. J. (Univ. South Florida Coll. Medicine, Tampa, FL, 33612); Boren, H. G. *Proc Am Assoc Cancer Res* 19: 136; 1978. (no refs)

**78-2095 Effects of Bile Acids on Induced Colon Cancer in Rats (Meeting Abstract).** (Eng) Cohen, B. I. (Public Health Res. Inst., Manhattan Veterans Admin. Hosp., New York, NY); Raicht, R. F.; Deschner, E. E.; Fazzini, E.; Takahashi, M.; Sarwal, A. *Proc Am Assoc Cancer Res* 19: 48; 1978. (no refs)

**78-2096 Cell Cycle Variation in Susceptibility to Hepatocarcinogenesis by MNU (Meeting Abstract).** (Eng) Kaufman, D. G. (Univ. North Carolina Sch. Medicine, Chapel Hill, NC, 27514); Kaufmann, W. K.; Rice, J. M.; Wenk, M. L. *Proc Am Assoc Cancer Res* 19: 183; 1978. (no refs)

**78-2097 Induction of Putative Initiated Hepatocytes by N-Methyl-N-nitrosourea (MNU) and Partial Hepatectomy (PH) (Meeting Abstract).** (Eng) Cayama, E. J. (Dept. Pathology, Univ. Toronto, Toronto, M5S 1A8, Ontario, Canada). *Proc Am Assoc Cancer Res* 19: 41; 1978. (1 ref)

**78-2098 Basal Mutagenic Activity (BMA) of Clinical Chloroethylnitrosoureas (NU), and the Effect of Microsomal Activation (Meeting Abstract).** (Eng) Franza, B. (Vincent T. Lombardi Cancer Res. Center, Georgetown Univ. Sch. Medicine, Washington, DC, 20007); Schein, P.; Saslaw, L.; Oeschger, M. *Proc Am Assoc Cancer Res* 19: 234; 1978. (1 ref)

**78-2099 A Comparative Study on the Mutagenicity of Ethylenethiourea in Bacterial and Mammalian Test Systems.** (Eng) Schupbach, M. (Biological and Pharmaceutical Dept., F. Hoffman-La Roche and Co., Ltd., Basel, Switzerland); Hummler, H. *Mutat Res* 56(2): 111-117; 1977.

The mutagenic effects of ethylenethiourea (ETU) were studied in several bacterial and mammalian test systems. Except in *Salmonella typhimurium* strains TA1530, 1531, 1532, and 1964, a 2-fold increase in the number of histidine revertants was not observed with TA1530; the other strains did not differ significantly from controls. Thus, ETU induces mutations of the base-pair substitution type. With strain hisG46, no increase in the number of revertant colonies was observed with ETU concentrations of 20-80 mg/plate. With TA1530, however, doses of 0.2-80.0 mg/plate resulted in a dose-dependent increase in the number of revertants. In a host-mediated assay with hisG46 and TA1530 and doses up to 6,000 mg/kg, no increase in reversion frequency was noted with the former, but only at the highest dose was a significant increase in reversion frequency noted with the latter. The results of the micronucleus test were negative after twofold po applications of 750, 1,850, and 6,000 mg/kg ETU to Swiss albino mice, indicating minimal chromosomal damage in the bone marrow. No dominant lethal effects were observed in male mice after single po doses of 500, 1,000, or 3,500 mg/kg. (33 refs)

**78-2100 Induction of Sister Chromatid Exchanges in Chinese Hamster Cells by Chlorpropamide (Meeting Abstract).** (Eng) Brown, R. F. (Dept. Biology, Southwest Texas State Univ., San Marcos, TX, 78666); Wu, Y. *Mutat Res* 56(2): 215-217; 1977.

The mutagenic capacity of chlorpropamide (250, 500, and 750 µg/ml) was investigated in Chinese hamster V79 cells. Chlorpropamide was mutagenic, as judged by a dose-dependent increase in the number of sister chromatid exchanges following treatment. Since the S-9 liver extract was not used, it is suggested that the parent compound is the mutagen. (7 refs)

**78-2101 Heterotopically Transplanted Rat Urinary Bladder as a Model for Bladder Carcinogenesis Study (Meeting Abstract).** (Eng) Oyasu, R. (Northwestern Univ. Medical Sch., Chicago, IL, 60611); Iwasaki, T.; Roeland, R.; Tabuchi, Y. *Proc Am Assoc Cancer Res* 19: 117; 1978. (1 ref)

**78-2102 Production of Mutagens by Nitrosation of Japanese Fish Sanma Hiraki (Meeting Abstract).**



act). (Eng) Mower, H. F. (Univ. Hawaii Sch. Medicine, Honolulu, HI, 96821); Weisburger, J. H. *Proc Am Assoc Cancer Res* 19: 89; 1978. (1 ref)

2103 **N-Methyl-N-nitrosourea Mediated Conversion of O<sup>6</sup>-Methylguanine to Xanthine (Meeting Abstract).** (Eng) Rao, P. M. (Depts. Pathology and Medical Genetics, Univ. Toronto, Toronto, Ontario M5S 1A8, Canada); Rajalakshmi, S.; Krepinsky, J.; Sarma, D. S. *Proc Am Assoc Cancer Res* 19: 39; 1978. (no refs)

2104 **Alkylation of DNA Oxygen Atoms by Nitrosoureas (Meeting Abstract).** (Eng) Jensen, D. (Oregon State Univ., Corvallis, OR, 97331). *Proc Am Assoc Cancer Res* 19: 238; 1978. (no refs)

2105 **Studies on DNA Repair in Frog and Human Cells Exposed to an Acridine Half-Mustard (ICR 191) and to MNNG.** (Eng) Viceps-Madore, D. (Inst. Cancer Res., 7701 Burholme Ave., Philadelphia, PA, 19111); Zger-Freed, L. *Mutat Res* 49(3): 407-419; 1978.

The effects of ICR 191 (2-methoxy-6-chloro-9-[3-(ethyl-2-thioethyl)aminopropylamino]acridine dihydrochloride) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) on DNA repair in frog and human cell cultures were measured autoradiographically as unscheduled DNA synthesis. Concentrations of  $10^{-3}$  to  $10^{-7}$  M ICR 191 failed to induce repair, determined by two criteria. Of 400 nuclei examined for each concentration, the percentage of labeled nuclei did not increase up to 18 days after treatment. Secondly, a new class of lightly labeled nuclei did not appear. By these criteria, however, MNNG stimulated unscheduled DNA synthesis in both frog and human fibroblast populations at  $10^{-4}$  to  $10^{-6}$  M. The intracellular localization of ICR 191 was examined by fluorescence microscopy, which showed preferential interaction with the lysosomes rather than with the genome of diploid cells. The repair and fluorescence studies indicate that the primary intracellular localization of ICR 191 takes place outside the genome in these eukaryotic cells. (39 refs)

2106 **Development of Neoplasia After In Vitro Exposure of Human Diploid Cells to Chemical Carcinogen (Meeting Abstract).** (Eng) Milo, G. E. (Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH, 43210); DiPaolo, J. A. *Proc Am Assoc Cancer Res* 19: 67; 1978. (no refs)

78-2107 **Stages of Carcinogenesis During Chemical Carcinogen Induced Neoplastic Transformation of Guinea Pig Cells in Culture (Meeting Abstract).** (Eng) Evans, C. H. (NCI, Bethesda, MD, 20014); Pomponio, J. M.; DiPaolo, J. A. *Proc Am Assoc Cancer Res* 19: 27; 1978. (no refs)

78-2108 **Influence of Duodenal Reflux on the Mucosa Near a Gastroenteral Anastomosis.** (Ger) Schlag, P. (Abteilung für Allgemeine Chirurgie des Departments für Chirurgie, Steinhovelstrasse 9, Universität Ulm, D-7900 Ulm, W. Germany); Meister, H.; Feyerabend, G.; Merkle, P. *Langenbecks Arch Chir* 344(3): 207-217; 1977.

The effects of N-methyl-N-nitrosoguanidine (MNG) and duodenogastric reflux on the gastric mucosa were studied in germfree male adult Wistar rats. The animals received MNG from the 5th to the 35th-36th postoperative week in doses that did not induce carcinomas in normal animals within 29-31 wk. Thirty animals underwent gastrotomy, 15 of which received MNG. Autopsy performed after 35-36 wk revealed the formation of fibrous tissue at the site of the gastrotomy, but an intact gastric mucosa. Carcinomas were not found. There was no difference between the MNG-treated and untreated groups. Thirty animals underwent gastroenterostomy without enteral anastomosis, and 15 of the animals received MNG. No differences were found between the treated and untreated groups. Polypous tumors were seen near the anastomosis in 17 animals, subserosal polypous changes (adenoma like proliferation with atypical epithelial regeneration) in 10. Thirty animals underwent Roux-en-Y anastomosis, which prevents the permanent reflux of bile and pancreatic juice, and 15 received MNG. Glandular regeneration was seen in 2 animals, an adenoma like proliferation in 4. Further away from the mouth of the anastomosis, atypical epithelial regeneration was seen in some animals, and an infiltrating adenopapillary carcinoma was found in one. This tumor may have developed as a result of the increased vulnerability of the mucosa, caused by the activation of MNG in the alkaline medium. Thus, the incidence and intensity of mucosal proliferation were considerably higher after gastroenterostomy without enteral anastomosis than after Roux-en-Y anastomosis, regardless of MNG treatment. This indicates that permanent reflux of bile and pancreatic juice is involved in the genesis of proliferative changes in the epithelium and, ultimately, of carcinoma in the resected stomach. (23 refs)

78-2109 **Ultrastructural Alterations of N-Methyl-N-nitroso-N'-nitroguanidine (MNNG)-treated Pancreatic Ductal Explants (Meeting Abstract).** (Eng) Jones, R. T. (Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201); Hudson, E. A.; Harris, C. C.; Trump, B. F. *Proc Am Assoc Cancer Res* 19: 47; 1978. (1 ref)



- 78-2110 **S-Phase Related Cytotoxicity of 10T 1/2 Cells to MNNG (Meeting Abstract).** (Eng) Grisham, J. W. (Dept. Pathology, Univ. North Carolina, Chapel Hill, NC, 27514); Greenberg, D. S.; Kaufman, D. G. *Proc Am Assoc Cancer Res* 19: 184; 1978. (no refs)

- 78-2111 **Mechanism of Potent Mutagenic Action of N-Methyl-N'-nitro-N-nitrosoguanidine on Intracellular Phage Lambda.** (Eng) Yamamoto, K. (Dept. Fundamental Radiology, Faculty Medicine, Osaka Univ., Kitaku, Osaka 530, Japan); Kondo, S.; Sugimura, T. *J Mol Biol* 118(3): 413-430; 1978.

The mechanism of action of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) on  $\lambda$  phage in *Escherichia coli* K12 strains was investigated. MNNG treatment produced a mutant  $\lambda$  phage yield about 100 times higher than the spontaneous yield following transfection of MNNG-treated spheroplast cells; the yield diminished an order of magnitude when untreated spheroplasts were assayed. Labeled MNNG treatment indicated that the  $\lambda$  DNA was methylated to no more than 0.6% by an MNNG dose of 0.09 mg/ml and was highly mutated.  $\lambda$  phages treated in vitro with ethyl methanesulfonate produced a low mutant yield on untreated cells, but the yield increased about tenfold on MNNG-treated cells. Mutability of untreated  $\lambda$  on cells having received an F' factor was enhanced efficiently by UV light but not by MNNG previously applied to the F'. Similar MNNG dose-effect curves were found for enhancing spontaneous, mispairing and misrepair mutagenesis of  $\lambda$ . It is concluded that MNNG hypermutagenesis results from a synergistic increase in mispairing probability of appropriately methylated bases in the target gene within an MNNG-induced intracellular environment that has an enhanced mutagenic capacity. (67 refs)

- 78-2112 **Mutagenicity Testing of H-193, AF-2 and Furazolidone in *Drosophila melanogaster*.** (Eng) Blijleven, W. G. (Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Labs., State Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands); Kortseus, M. J.; Kramers, P. G. *Mutat Res* 56(1): 95-100; 1977.

The mutagenicity of the antibacterial food additives 5-nitro-2-(p-carbamoylstyryl)furane (H-193) and 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) and of furazolidone, a drug and coccidiostatic agent, was evaluated in *Drosophila melanogaster*. Possible genetic effects were measured using a technique that determines the induction of sex-linked recessive lethals. H-193 consistently produced a weak enhancement of the mutation frequency without an apparent relationship to the exposure level used. AF-2 produced increased mutation rates in two experiments, but the mutagenic effects could hardly be reproduced in two other tests. Furazolidone produced a consistent increase in the frequency of sex-linked

recessive lethals. The specific sensitivity of spermatids appeared to be a common feature of all three nitrofurans. The failure to obtain higher mutation frequencies as well as the observed inconsistencies are to be expected with poorly water-soluble compounds. With such compounds, the highest possible concentration in solution sets a limit to the exposure level that can be applied. For the compounds tested, these limits are apparently quite close to the lowest effective concentration. (12 refs)

- 78-2113 **Comparisons of Mutation Induction in Reversion Systems of *Saccharomyces cerevisiae* and *Salmonella typhimurium*.** (Eng) Shahin, M. M. (Dept. Genetics, Univ. Alberta, Edmonton, Alberta, Canada T6G 2E9); Von Borstel, R. C. *Mutat Res* 53(1): 1-10; 1978.

The mutagenic responses of the *Salmonella typhimurium* and *Saccharomyces cerevisiae* assay systems to furylfuramide (AF-2), SQ18,506, 1,2-diamino-4-nitrobenzene, 1,4-diaminoanthraquinone, methyl violet, and ethyl methanesulfonate were investigated. With *S. typhimurium*, 1,2-diamino-4-nitrobenzene, AF-2 (only at 0.02  $\mu$ g/plate), and ethyl methanesulfonate were mutagenic. With the yeast assay, ethyl methanesulfonate was mutagenic under both the soft-agar and nonnutrient conditions; AF-2 and SQ18,506 induced mutations in *S. cerevisiae*, but only when the nonnutrient procedure was used. The toxicity of 1,2-diamino-4-nitrobenzene, 1,4-diaminoanthraquinone, and methyl violet was then tested using *S. cerevisiae*. Methyl violet was the most toxic followed by 1,4-diaminoanthraquinone; this observation held under both soft-agar and nonnutrient conditions. These results do not support the assumption that yeast mutagenic systems are less sensitive than the reversion system of *S. typhimurium*. (14 refs)

- 78-2114 **Mutagenicity of an Antitumor Protein, Neocarzinostatin, in *Escherichia coli*.** (Eng) Tatsuno, K. (Dept. Microbiology, Univ. Chicago, Chicago, IL, 60637); Nishioka, H. *Mutat Res* 56(1): 91-94; 1977.

The mutagenic and growth inhibition effects of the antitumor protein neocarzinostatin (NCS) were tested in *Escherichia coli*. Possible growth inhibition of *E. coli* by NCS was studied using a simple streak test. The inhibition zone caused by either NCS or 4-nitroquinoline N-oxide (4NQO) was greater with *E. coli* WP100, a DNA repair-deficient strain, than with strain WP3, a repair-proficient strain. Kanamycin, a nonmutagenic antibiotic, inhibited the growth of both strains to a similar extent. This suggests that NCS induces damage to DNA as effectively as does 4NQO, a typical mutagen. In a standard mutagenicity spot test NCS induced reversion mutations involving base-pair substitution. These results suggest that NCS induced repairable DNA damage that led either to mutation or death as a result of either direct



direct interaction with cellular DNA. Since chemicals mutagenic in the bacterial test system may be carcinogenic, 2-aminofuran should be suspected as a carcinogen. (24 refs)

78-2115 **Mutagenic Activities of Nitrofurans in *Neurospora crassa*.** (Eng) Ong, T. M. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709). *Mutat Res* 56(1): 13-20; 1977.

The mutagenicity and mutagenic specificity of 12 nitrofurans were studied in the adenine-3 (ad-3) test system of *Neurospora crassa*. Conidia of *N. crassa* were treated with various concentrations of the nitrofurans for 2 hr in the dark, the ad-3 mutants were isolated, and mutation frequencies were determined. Under these conditions, 2-formylamino-4-(5-nitro-2-ethylthiazole) (FANFT), trans-5-amino-3-[2-(5-nitro-2-ethylvinyl)]1,2,4-oxadiazole (<sup>3</sup>Q18506), and 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) were potent mutagens for *N. crassa*. 5-Nitro-2-(p-carbamoylstyryl)furan (H-193) was a moderate mutagen, and 5-nitro-2-furaldehyde semicarbazone (nitrofurazon) and N-isopropyl-3-(5-nitro-2-ethylacrylamide) (F30066) were weak mutagens. The other compounds were not mutagenic in *Neurospora*. Nitrofurans, AF-2, FANFT, and SQ18506 are all carcinogenic in laboratory mammals, but there are no carcinogenicity data for H-193 and F30066. Since previous studies have shown a positive correlation between carcinogenicity and mutagenicity in *N. crassa*, H-193 and F30066, the antischistosomal drugs, might also be carcinogenic. Structure/activity correlations studies indicated that the NO<sub>2</sub> group at the C5 position of the furan ring and the side chain at the C2 position are necessary for the mutagenic activity of these nitrofurans and that the latter is more specific for this activity. (22 refs)

78-2116 **Mutagenicity of N-Nitrosopiperidines with *Salmonella typhimurium* Microsomal Activation System.** (Eng) Rao, T. K. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Hardigree, A. A.; Young, J. L.; Lijinsky, W.; Epler, J. L. *Mutat Res* 56(2): 131-145; 1977.

The mutagenicity of N-nitrosopiperidine and its various substituted derivatives was investigated in strains of *Salmonella typhimurium* with and without microsomal activation. With the missense mutant TA1535 and no metabolic activation, only 2/19 compounds (3,4-dibromonitrosopiperidine and nitroso-1,2,3,6-tetrahydropiperidine) had high mutagenic activity. Nitroso-4-piperidone and 3,4-dichloronitrosopiperidine exhibited significant but small mutagenic activity in the spot test. Studies with various strains indicated that TA1535 had the greatest ability to detect mutagens. N-nitrosopiperidine was found to possess mutagenic activity upon activation with rat liver microsomes; phenobarbital-induced preparations gave max activity. Tests with the substituted derivatives indicated that the carbon

atoms  $\alpha$  to the N-nitroso group are important, since blockage of these positions reduced or eliminated both the mutagenicity and carcinogenicity of nitrosopiperidine. (20 refs)

78-2117 **Localization of Alpha<sub>1</sub>-Fetoprotein and DNA-Synthesis in Liver Cell Populations During Experimental Hepatocarcinogenesis in Rats.** (Eng) Kuhlmann, W. D. (Immunocytochemistry SFB 136, Institut für Nuklearmedizin/D.K.F.Z., Heidelberg, W. Germany). *Int J Cancer* 21(3): 368-380; 1978.

The localization of cellular  $\alpha_1$ -fetoprotein (AFP) was investigated in 6-, 12-, and 20-wk-old rats fed N-nitrosomorpholine (NNN) at doses of 6 mg/kg/day for 12 wk or 20 mg/kg/day for 6 wk. The oldest rats were fed only the higher dose. Regardless of age, both NNN schedules resulted in hepatomas, and during the early stages of hepatoma induction, the histotoxic patterns depended on dose. Necrosis of hepatocytes and proliferation of small, oval-shaped cells occurred with the high doses. Parallel to the proliferation of the oval-shaped cells, there was an increase in serum AFP levels. Immunoperoxidase staining revealed that AFP production was confined to the oval-shaped cells. In pulse-chase labeling experiments with <sup>3</sup>H-thymidine, oval-shaped cells were seen to be developing into mature hepatocytes, and distinct areas with a hyperplastic appearance were observed. Normal hepatocytes and hyperplastic areas did not stain for AFP. At low doses of NNN, no cellular or serum AFP was detected unless hepatoma cells had developed. During malignant transformation, distinct AFP-staining nodules consisting of neoplastic hepatocytes were localized. Pulse-chase labeling experiments demonstrated the proliferative character of these hepatoma cells. There was no correlation between the presence of AFP and the histology of the tumor. The wide range of serum AFP levels and their rates of increase in individual rats indicated the heterogeneous character of the tumors with respect to AFP production. (48 refs)

78-2118 **A Model System for the Formation of N-Nitrosopyrrolidine in Grilled or Fried Bacon.** (Eng) Coleman, M. H. (Unilever Res. Lab., Colworth House, Sharnbrook, Bedford, England). *J Food Technol* 13(1): 55-69; 1978.

The occurrence of N-nitrosopyrrolidine (NNP) in bacon and pork products was investigated, and a model system for its formation in bacon was devised. NNP was formed only during grilling or frying, it was not found in raw bacon or in boiled ham. NNP formation was mainly limited to the fatty tissue, which reached a higher temperature than the lean meat during cooking. More than 92% of the total nitrosamines and > 99% of the NNP was found in the fatty portion. Furthermore, heating of the bacon alone resulted in NNP formation. Heating of pork fat alone resulted in no increase



in NNP content, but the pyrrolidine content was increased; this increase was more than sufficient to account for the NNP content in bacon. Since this pyrrolidine was readily nitrosated in the presence of nitrite, it is suggested that proline is a likely precursor of NNP. In the model experiment, a reaction mixture of 800 ppm proline and 200 ppm sodium nitrite in methanol was heated in an oil bath for 1 hr at 170 C. Water exerted an inhibitory effect on nitrosamine formation both in the model system and in actual heating tests. Ethoxyquin inhibited nitrosamine formation in the model system. The requirement for a high temperature, the inhibitory effects of water and antioxidants, and the catalytic effect of a lipid hydroperoxide are consistent with the involvement of a free radical in the formation of NNP. (29 refs)

**78-2119 Fecal Mutagens: A Possible Relationship with Colorectal Cancer (Meeting Abstract).** (Eng) Land, P. C. (Ontario Cancer Inst., Toronto, Ontario, Canada); Bruce, W.R. *Proc Am Assoc Cancer Res* 19: 167; 1978. (1 ref)

**78-2120 Effect of Dose on N-[4-(C5-Nitro-2-Furyl)-2-Thiazolyl] Formamide (FANFT) Induced Urinary Bladder Carcinogenesis in Rats (Meeting Abstract).** (Eng) Jacobs, J. B. (Dept. Pathology, St. Vincent Hosp., Worcester, MA, 01504); Cohen, S. M.; Friedell, G. H. *Proc Am Assoc Cancer Res* 19: 4; 1978. (no refs)

**78-2121 Binding of 2-Amino-4-(5-nitro-2-furyl)-2-<sup>14</sup>C-thiazole (ANFT) to Rat Liver Microsomes (Meeting Abstract).** (Eng) Swaminathan, S. (Dept. Human Oncology, Univ. Wisconsin Medical Sch., Madison, WI, 53706); Lower, G.M.; Bryan, G.T. *Proc Am Assoc Cancer Res* 19: 150; 1978. (no refs)

**78-2122 Carcinogenicity of 2-Amino-4-(5-nitro-2-furyl)thiazole in Rats and Metabolism of this Carcinogen by Cultured Dog Urothelial Cells (Meeting Abstract).** (Eng) Wang, C. Y. (Dept. Human Oncology, Univ. Wisconsin Center Health Sciences, Madison, WI, 53706); Kamiryo, Y. *Proc Am Assoc Cancer Res* 19: 146; 1978. (no refs)

**78-2123 Evaluation of the Mutagenic Potential of Mycotoxins Using *Salmonella Typhimurium* and *Saccharomyces cerevisiae*.** (Eng) Kuczuk, M. H. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS, 39216); Benson, P. M.; Heath, H.; Hayes, A. W. *Mutat Res* 53(1): 11-20; 1978.

The mutagenicity of aflatoxin B<sub>1</sub>, citrinin, diacetoxyscirpenol, griseofulvin, ochratoxin A, an ochratoxin A and mixture, oosporein patulin, penicillic acid, penitrem A, sterigmatocystin, T-2 toxin, verruculogen, viriditoxin, and zearalenone was investigated in two in vitro microbial test systems using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* strain D-3. The compounds were tested at doses of 0.1 to 10 µg/plate. In the absence of a hepatic S-9 activation system, none of the mycotoxins were mutagenic in either species. In the activated *S. typhimurium* system, however, aflatoxin B<sub>1</sub>, sterigmatocystin, and ochratoxins A + B were mutagenic. With the activated yeast test system, only aflatoxin B<sub>1</sub> and sterigmatocystin were mutagenic. (26 refs)

**78-2124 Aflatoxin Content in Oil Seed Remnants after Oil Extraction.** (Ger) Dietrich, H. (Staat. Landwirtschaftl. Versuch.-und Forschungsanst. Austenberg, Nusslerstrasse 23, D-7500 Karlsruhe 41, W. Germany); Hoffmann, G. *Landwirtschaftl Forsch* 31(1): 19-25; 1978.

The aflatoxin content was investigated in various seeds after extraction of their oil. Aflatoxins were found in tropical and subtropical seeds, but their average levels were 33 ppb (coconut), 26 ppb (cotton seeds), and 15 ppm (palm kernels), much lower than the levels found in peanut products (530 ppb). Plants found locally (Karlsruhe area of W. Germany) contained low aflatoxin levels: <5 ppb. (8 refs)

**78-2125 A Comparison of [<sup>14</sup>C]Aflatoxin B<sub>1</sub> and [<sup>14</sup>C]Aflatoxin G<sub>1</sub> Binding to Rat Liver Microsomes (Meeting Abstract).** (Eng) Garner, R. C. (Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, North Yorkshire, England); Nutman, C. A.; Sunman, V.; Martin, C. N. *Proc Am Assoc Cancer Res* 19: 171; 1978. (no refs)

**78-2126 Aflatoxin Inhibition of Avian Hepatic Mitochondria.** (Eng) Obidoo, O. (Dept. Biochemistry, Ahmadu Bello Univ., Zaria, Nigeria); Siddiqui, H. *Biochem Pharmacol* 27(4): 547-550; 1978.

The effect of aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) on electron transport and oxidative phosphorylation was examined polarographically in guinea fowl (*Numida meleagris* Pearl) hepatic mitochondria. Addition of AFB<sub>1</sub> to mitochondria actively respiring on various substrates resulted in inhibition of oxygen consumption. The degree and site(s) of inhibition depended on AFB<sub>1</sub> concentration, the presence or absence of ADP, the substrate used, but in all cases inhibition was not relieved by 2,4-dinitrophenol. The major sites of inhibition of electron transport are probably localized at the first and second phosphorylation sites. (10 refs)



orylation coupling sites. Inhibition may also occur at the cytochrome oxidase level, depending on the rate of respiration. These findings may explain the greater susceptibility of some avian species to aflatoxin toxicity. (13 refs)

2127 **Early Effects of Dietary Feeding of Aflatoxin B<sub>1</sub> on Hepatic Ribosomal RNA** (Meeting Abstract). (Eng) Deen, K. C. (Dept. Pharmacology, Pennsylvania State Univ., Hershey, PA, 17033); Smith, S. J. *Proc Am Assoc Cancer Res* 19: 170; 1978. (no refs)

2128 **Comparison of Potential Patulin Hazard in Home-made and Commercial Apple Products.** (Eng) Lindroth, S. (Food Res. Lab., Technical Res. Centre, Vammala, SF-02150 Espoo 15, Finland); Niskanen, A. *J Food Sci* 43(2): 446-448; 1978.

A thin-layer chromatographic procedure, using benzene-ethanol-acetic acid as the first developing solution and toluene-ethyl acetate-formic acid as the second, was developed for the determination of patulin concentrations in apple products. Of 900,000 kg of apple juice concentrate assayed, 100,000 kg contained patulin concentrations ranging from 50 to 690 µg/liter. Of 200,000 kg of apple flavor concentrate, 100,000 had patulin concentrations ranging from 10 to 1,770 µg/liter. Of 20 samples of homemade apple jam examined, 8 had patulin concentrations between 10 and 16,400 µg/liter. The frequency of patulin occurrence in commercial and homemade apple juices was 20 and 40%, respectively. In moldy homemade apple jam, patulin was found to have diffused to all levels of the jam. Ten samples of apples spontaneously affected by mold in the laboratory contained patulin; this indicates the prevalence of patulin-producing fungal strains. Patulin was found in apple cider, apple wine, apple vinegar, pear juice concentrate, or dried apricots. These findings indicate that patulin risk in homemade apple products is greater than in commercial apple products. (22 refs)

2129 **Simultaneous Production of Penicillic Acid and Patulin by a Penicillium Species Isolated from Cheddar Cheese.** (Eng) Olivigni, F. J. (Dept. Food Science and Technology, Univ. Nebraska-Lincoln, Lincoln, NE 68583); Bullerman, L. B. *J Food Sci* 42(6): 1654-1657, 1965; 1978.

The production of patulin and penicillic acid by culture of 47, a *Penicillium* species isolated from Cheddar cheese and tentatively identified as an atypical strain *Penicillium roqueforti*, was investigated. Growth on continuous incubation mixtures was measured at 5, 12, and 25 C. On potato-dextrose broth, patulin was pro-

duced at all three temperatures, but penicillic acid was produced in only small amounts at 12 C. On yeast extract sucrose broth, both patulin and penicillic acid were produced in relatively high concentrations at the two lower temperatures. At 25 C, however, there was no patulin and only a small amount of penicillic acid. With Raulin-Thom broth, trace amounts of patulin were detected at 12 and 25 C; penicillic acid was detected at all temperatures, but only in small amounts. With all three substrates, the optimum incubation temperature was 12 C; detectable toxin concentration decreased over time, and the reason for this is unknown. With lactose as a substrate, penicillic acid was produced only at 25 C. No patulin or penicillic acid production was noted on casein in the absence of carbohydrate, in spite of extensive mold growth. Cheddar cheese, Swiss cheese, summer sausage, and corn tortillas did not support detectable levels of either penicillic acid or patulin, whereas moistened cornmeal, yellow dent corn, and shredded wheat-nutrient broth substrates supported toxin production at all three temperatures. Once again, optimum production occurred at 12 C. (25 refs.)

78-2130 **2,3-Dihydro-2-(guan-7-yl)-3-hydroxy-aflatoxin B<sub>1</sub>, a Major Acid Hydrolysis Product of Aflatoxin B<sub>1</sub>-DNA or -Ribosomal RNA Adducts Formed in Hepatic Microsome-mediated Reactions and in Rat Liver In Vivo.** (Eng) Lin, J. K. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI 53706); Miller, J. A.; Miller, E. C. *Cancer Res* 37(12): 4430-4438; 1977.

DNA- and ribosomal RNA (rRNA)-bound aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) adducts obtained from salmon sperm DNA and rat liver rRNA with fortified rat and hamster liver microsomes were hydrolyzed with weak acid to yield 2,3-dihydro-2-(guan-7-yl)-3-hydroxy-AFB<sub>1</sub> as the major product. This product was characterized on the basis of its nuclear magnetic resonance, UV, and infrared spectra; its hydrolysis to guanine, 2,3-dihydro-2,3-dihydroxy-AFB<sub>1</sub>, and acid degradation products of the latter; its deamination to a product that yielded xanthine on hydrolysis; and the susceptibility of its nucleic acid precursors to hydrolysis in weak alkali. Acid hydrolysis of the nucleic acid-AFB<sub>1</sub> adducts also yielded 2,3-dihydro-2,3-dihydroxy-AFB<sub>1</sub> and two minor products, the amounts of which increased greatly if the nucleic acid adducts were previously exposed to weak alkali. One of the latter compounds was tentatively identified as 2,3-dihydro-2-(N<sup>5</sup>-formyl-2,5,6-triamino-4-oxopyrimidine-N<sup>5</sup>-yl)-3-hydroxy-AFB<sub>1</sub>. Hydrolysis of the hepatic DNA and rRNA from rats injected with <sup>3</sup>H-AFB<sub>1</sub> liberated tritiated products that cochromatographed on high-performance liquid chromatography in four solvent systems with the products obtained upon hydrolysis of the adducts formed in vitro. The sameness of the major products from the adducts formed in vivo and in vitro was further shown by the chromatographic identities of the derivatives formed on acetylation,



deamination, and acid hydrolysis of the two compounds. (47 refs.)

- 78-2131 Mutagenicity and Carcinogenicity of Tannin and Tannin-Free Fractions of Bracken Fern (BF) (Meeting Abstract).** (Eng) Hatcher, J. (Dept. Human Oncology, Univ. Wisconsin Center Health Sciences, Madison, WI, 53706); Pamukcu, A. M.; Wang, C. Y.; Bryan, G. T. *Proc Am Assoc Cancer Res* 19: 18; 1978. (no refs)

- 78-2132 Comparative Analysis of Mutagenic Activity of Curing Agents VNIIMP and Vakhtol. (Rus)** Karplyuk, I. A. (Dept. Hygiene and Nutrition, Central Inst. Advanced Training Physicians, Moscow, USSR); Gogol, A. T.; Okuneva, L. A.; Rybakova, K. D.; Zhurkov, V. S. *Vopr Pitan* (5): 89-92; 1977.

The mutagenic activity of two curing agents, VNIIMP and Vakhtol, used in the smoking of meat and fish, was tested in different experimental systems. The agents are the products of wood pyrolysis, and they contain acetic acid, phenols, and formaldehyde but no benzo(a)-pyrene. Incubation of the auxotrophic Thy- strain of *E. coli* K-12 with 1% Vakhtol increased the frequency of reverse mutations 3.5 times over control values. The mutagenic activity of VNIIMP was less pronounced; only large concentrations of the agent (25%) produced a twofold increase in the mutation rate. Incubation of Vakhtol (at  $0.5 \times 10^{-3}$  dilution) with a peripheral blood lymphocyte culture yielded 2.7% aberrant metaphases (compared to 1.0% in controls). It is recommended that the use of Vakhtol in the food industry be restricted. (2 refs.)

- 78-2133 Saccharin and Cyclamate in Human Bladder Cancer (Meeting Abstract).** (Eng) Kessler, I. I. (Johns Hopkins Univ., Baltimore, MD, 21205); Clark, J. P. *Proc Am Assoc Cancer Res* 19: 9; 1978. (no refs)

- 78-2134 Molecular Mechanism of Polyploidization and Binucleate Formation of the Hepatocyte. (Eng)** Nakanishi, K. (Dept. Pathology, Kyoto Prefectural Univ. Medicine, Kyoto, Japan); Fujita, S. *Cell Struct Funct* 2(3): 261-265; 1977.

A DNA cross-linking agent was administered to young rats, and the increase in polyploid and binuclear cells among the hepatocytes was examined to test the hypothesis that polyploidization and binuclear cell formation become manifest through abortive proliferation of a cell in which the

nucleus possesses cross-links between the DNA double strands. Actinomycin D (0.25  $\mu\text{g}/\text{animal}$ ) or mitomycin C (1  $\mu\text{g}/\text{g}$ ) was given ip to Donryu rats on alternate days from the second day after birth. At the end of the first, second, or third weeks after birth, the animals were given  $^3\text{H}$ -thymidine and then sacrificed. The rate of binuclear cell appearance in the hepatocytes was determined on section preparations, the degree of polyploidization by autoradiography. In rats receiving small quantities of actinomycin D for 1 wk, binuclear cells greatly increased; in rats given actinomycin D for 2 or 3 weeks, the percentage of binuclear cells remained almost unchanged, while that of polyploid cells increased significantly. The strong cross-linking agent, mitomycin C, caused more polyploidization in rats of all ages than did actinomycin D. These results support the cross-linking hypothesis, since the administration of the two cross-linking agents enhanced binucleate formation and polyploidization of hepatocytes. (15 refs)

- 78-2135 Mammary Tumors Induced in Rats by Adriamycin and Daunomycin. (Eng)** Solcia, E. (Pathological Anatomy, Univ. Pavia, Pavia, Italy); Bellini, O.; Sala, L.; Bertazzoli, C. *Cancer Res* 38(5): 1446; 1978.

The carcinogenicity of a single iv dose of adriamycin (AD) and daunomycin (DM) was investigated in virgin female Sprague-Dawley rats. The mice received either 6.25 or 12.5 mg/kg DM, or 4, 6.5, or 8 mg/kg AD. The rats were sacrificed when they showed palpable tumors or appeared moribund, or after 1 yr. With DM, mammary tumors developed in 6/7 low-dose and 37/65 high-dose animals. The incidences with 4, 6.5, and 8 mg/kg AD were 4/7, 4/10, and 39/63, respectively. The incidence of DM-induced adenocarcinomas increased with dose, but that of AD showed a peak at 6.5 mg/kg and above. AD- and DM-induced fibroadenomas showed a peak at the lower doses (5-6 mg/kg). With DM, there was a slight prevalence of adenocarcinoma over fibroadenomas at the highest dose. These results confirm the high oncogenic potential of AD and DM. (5 refs)

- 78-2136 Betamethasone-induced Leukaemoid Reaction in Pre-term Infant (Letter to Editor).** (Eng) Lawski, D. (Div. Perinatal Medicine, Dept. Pediatrics, Mount Sinai Medical Center, Long Branch, NJ, 07740); Hegyi, T. *Lancet* 1(8057): 218-219; 1978.

A leukemoid reaction was noted in a preterm (30-wk) infant born to a 21-yr-old woman. Four hours prior to delivery the woman had been given 12 mg betamethasone. Differential blood counts revealed a leukemoid reaction on the 1-11 of life. Since the reaction could not be attributed to other causes, it is suggested that the betamethasone treatment had triggered it. (2 refs)



8-2137 **Effects of Some Ergot Derivatives in Bone Marrow of Mice.** (Eng) Roberts, G. T. (Dept. Pharmacology, Univ. Melbourne, Parkville, 3052, Australia); Rand, M. J. *Mutat Res* 56(1): 59-67; 1977.

Dihydroergotoxine mesylate, ergotamine tartrate, and methysergide hydrogen maleate were tested for their cytogenetic effects on mouse bone marrow. The three test substances and cyclophosphamide, which was included as a positive control, were injected ip in H.P.F. Fullinsdorf male mice in doses of 25, 50, and 100 mg/kg. The mice were inoculated twice, 4 hr apart; colchicine was also injected at the second treatment. The animals were killed 6 hr after the second injection, and bone marrow specimens were prepared for cytogenetic analysis. No chromosome damage was caused by the lowest dose of the ergot derivatives. At 50 mg/kg, dihydroergotoxine and methysergide produced significant chromosome damage, but ergotamine did not. Significant numbers of aberrations were observed in all bone marrow preparations after treatment of the mice with 100 mg/kg of ergot derivatives. Almost all the damage was in the form of chromatid aberrations. The frequency of damage was 7 to 10 times less than that produced by cyclophosphamide. The ergot derivatives, therefore, have weak chromosomal damaging effect in vivo only at very high doses. It is unlikely that this effect would occur to a significant extent with the doses (2-6 mg/day) used therapeutically in humans. (22 refs)

8-2138 **Early Steps in Hycanthone-induced Mutagenesis (Meeting Abstract).** (Eng) Neubort, S. (Albert Einstein College Medicine, Bronx, New York, NY, 10461); Liebeskind, D.; Kozin, A.; Bases, R. *Proc Am Assoc Cancer Res* 19: 21; 1978. (no refs)

8-2139 **Early Steps in Mutagenesis by Hycanthone.** (Eng) Bases, R. (Dept. Radiology, Albert Einstein Coll., 1300 Morris Park Ave., Bronx, NY, 10461); Mendez, F.; Elequin, F.; Liebeskind, D.; Kozin, A.; Neubort, S. *Cancer Res* 38(3): 781-786; 1978.

The mutagenicity of hycanthone in HeLa cells was investigated and compared to that of eight other thioxanthones. HeLa cells were exposed to 3 µg/ml hycanthone for 30-40 min and the levels of immunoreactivity examined. High levels of reactivity were initially observed, but when hycanthone was removed, the cells returned to normal G<sub>1</sub> levels of reactivity in approx 1 hr. Experiments with labeled hycanthone and exponentially growing HeLa cells indicated that the mutagen does not covalently bind to DNA, ribosomal RNA, tightly bound nonhistone chromatin proteins, or any of the major polar lipid fractions. Furthermore, no effect on the sedimentation of cell lysate DNA was noted. A comparison with other thioxanthones indicated that hycanthone was the most potent mutagen and that it induced a strong im-

munoreactivity response without inhibiting protein synthesis. Lucanthone and some other thioxanthones that did not inhibit protein synthesis did not induce immunoreactivity and they were weak mutagens. Results obtained with lucanthone, IA-3, and IA-3-N oxide suggest that RNA synthesis inhibition itself does not induce immunoreactivity to antinucleoside antibodies. Immunoreactivity induction in the absence of protein synthesis inhibition correlated best with mutagenicity in this series. Radioautography determinations indicated that hycanthone did not induce DNA repair synthesis. Hycanthone (3 µg/ml) also induced immunoreactivity in fibroblasts from three normal subjects and seven patients with DNA repair deficiencies. (34 refs)

78-2140 **Mepartricin, a Polyene Active on both *Trichomonas* and *Candida*. Lack of Mutagenic Activity.** (Eng) Ruozzi, P. (Centro di Ricerche Cliniche Della Spa, Milan, Italy); Siccardi, A. G. *Farmaco [Sci]* 33(1): 21-25; 1978.

The mutagenic effect of mepartricin, an antibiotic active against *Trichomonas* and *Candida*, was investigated using *Salmonella typhimurium* strains TA1535, TA100, TA1538, and TA98. No mutagenic activity was noted. This drug can be used as a safer alternative to metronidazole. (17 refs)

78-2141 **Induced Cytogenetic Abnormalities by ICR-191 (Meeting Abstract).** (Eng) McGeorge, L. (Inst. Medical Res., Camden, NJ, 08103); Nichols, W. W.; Bradt, C. I.; Jacobs, L.; Minter, J. *Proc Am Assoc Cancer Res* 19: 218; 1978. (no refs)

78-2142 **Transformation of Human Neuroblastoma Cells into Ganglion Cells In Vitro with Mitomycin-C (Meeting Abstract).** (Eng) Goldstein, M. N. (Washington Univ. Sch. Medicine, St. Louis, MO, 63110). *Proc Am Assoc Cancer Res* 19: 28; 1978. (no refs)

78-2143 **The Influence of Caffeine on the Mitomycin C-induced Chromosome Aberration Frequency in Normal Human and Xeroderma Pigmentosum Cells.** (Eng) Hartley-Asp, B. (A B Leo Res. Labs., Fack, S-251 00 Helsingborg, Sweden). *Mutat Res* 49(1): 117-126; 1978.

The clastogenic action of mitomycin C (MC), alone and in combination with caffeine, was determined in normal human fibroblasts (F2000 or 1BR) and in xeroderma pigmentosum (XP) cells of both classical (XP4LO) and variant origin (XP7TA). Treatment of cells with 0.1 µg/ml MC produced



a higher frequency of aberrations in the classical line than in either the variant XP or the normal human cell lines. This was due to an increase in the frequency of chromatid breaks and exchanges. With caffeine posttreatment ( $2.5 \times 10^{-4}$  M), potentiation of the MC-induced aberration frequency occurred in all lines at concentrations  $> 2.5 \times 10^{-4}$  M. The variant had a higher sensitivity to caffeine than the classical XP or the normal human cell lines. This was due to a threefold increase in the frequency of chromatid breaks. These findings support the assumption that postreplication repair is the most sensitive of the repair systems to caffeine and that processes involved in the repair of MC-induced damage in all types of cells are susceptible to caffeine inhibition. (40 refs)

**78-2144 Acute Leukaemia after Alkylating Agents (Meeting Abstract).** (Eng.) Bell, R. (Special Haematology Clinic, Dept. Haemato-Oncology, Royal Melbourne Hosp., Victoria, Australia); Sullivan, J. R.; Hurley, T. H. *Aust NZ J Med* 7(5): 570; 1977. (no refs)

**78-2145 In Vitro Testing of an Indirect Mutagen (Cyclophosphamide) with Human Leukocyte Cultures: Activation with Liver Microsomes and Use of a Dialysis Bag.** (Eng) Madle, S. (Institut für Genetik, Freie Universität Berlin, Arnimallee 5-7, 1000 Berlin 33, W. Germany); Obe, G. *Mutat Res* 56(1): 101-103; 1977.

The mutagenicity of cyclophosphamide (CP) in human lymphocytes was investigated using a dialysis bag containing S-9 + CP submerged in the medium. Both induction of chromatid translocations and reduction of the mitotic index were greater after activation than before. Use of the dialysis bag reduces the toxic activity of the S-9 constituents on the lymphocytes and makes sterilization of the test substances unnecessary. (18 refs)

**78-2146 In Vitro Testing of an Indirect Mutagen (Cyclophosphamide) with Human Leukocyte Cultures. Activation by a Non-enzymatic Hydroxylation System (Udenfriend System).** (Eng) Madle, S. (Institut für Genetik, Freie Universität Berlin, Arnimallee, D 1000 Berlin 33, W. Germany); Obe, G. *Mutat Res* 49(1): 149-151; 1978.

The ability of cyclophosphamide to induce mutations in in vitro cultures of human WBC was investigated following its activation by a nonenzymatic hydroxylation system (Udenfriend system; UFS). The UFS consisted of 20 mM ascorbic acid, 2 mM Na-EDTA, 1 mM  $\text{FeSO}_4$ , and 66 mM phosphate buffer (pH 7.2). The UFS (10 ml) was allowed to react with 10 mM CP in the presence of air; various concentrations of

the UFS-CP mixture were added to 2.5 ml of WBC to achieve CP concentrations in culture of 2.9, 1.5, 0.8, and 0.4 mM. UFS alone led to the induction of only a few translocations but at a concentration of 28.6%, it suppressed the mitotic index (MI) approx 50%. At all concentrations, CP alone had no influence on MI. In the UFS-CP system, induction of MI increased with decreasing CP concentration and the highest number of translocations was noted in cells receiving 1.4 mM CP. Of 192 translocations, 94 were symmetric and 98 were asymmetric. (14 refs)

**78-2147 Cytoxan Induced Oncogenic Transformation: Chromosome Breakage and Sister Chromatid Exchange (SCE) Following Microsomal Activation (Meeting Abstract).** (Eng) Benedict, W. F. (Childrens Hosp. of Los Angeles, Los Angeles, CA, 90027); Banerjee, A. *Proc Am Assoc Cancer Res* 19: 91; 1978. (1 ref)

**78-2148 Frequency of Cyclophosphamide-induced Chromosome Aberrations in Murine Bone Marrow Cells.** (Rus) Zhurkov, V. S. (A.N. Sysin Inst. Genet. and Communal Hygiene, Moscow, USSR); Novakova, I. I.; Shram, R. I. *Gig Sanit* (1): 12-14; 1978.

The incidence of chromosome aberrations in the bone marrow cells of random-bred mice exposed to cyclophosphamide (0.01% soln in drinking water) for 1-70 days was 10.5% on day 11 and 19.6% on day 28 (vs 2.6% in controls). (12 refs)

**78-2149 Mechanism of Action of Estrogen(E): A Component (Meeting Abstract).** (Eng) Soto, M. (Tufts Univ. Sch. Medicine, Boston, MA, 02111); Soto, M.; Schein, C. *Proc Am Assoc Cancer Res* 19: 27; 1978. (1 ref)

**78-2150 Estrogen-Induction of Specific Growth Factors for Hormone-responsive Mammary, Pituitary, and Kidney Tumor Cells (Meeting Abstract).** (Eng) Sirb, D. A. (Univ. Texas Medical Sch., Houston, TX, 77025). *Am Assoc Cancer Res* 19: 8; 1978. (no refs)

**78-2151 Regulation of In Vitro Growth of Human Melanoma Cell Line by Steroid Hormones (Meeting Abstract).** (Eng) Walker, M. J. (Univ. Ill.



Medical Center, Chicago, IL, 60612); Chaudhuri, P. K.; Tito, J.; Snyder, J.; Das Gupta, T. K. *Proc Am Assoc Cancer Res* 19: 10; 1978. (no refs)

78-2152 **Reserpine and Breast Cancer.** (Eng) Kodlin, D. (Dept. Biometry, Louisiana State Univ. Medical Center, 1542 Tulane Ave., New Orleans, LA, 70112); McCarthy, N. *Cancer* 41(2): 761-768; 1978.

The association between reserpine use and breast cancer was investigated in 108 hypertensive breast cancer patients and 104 hypertensive controls, matched by year of birth and race. Although the crude data showed a significant positive association between reserpine use and breast cancer, the association disappeared after further matching with respect to the year of first hypertension diagnosis and the subsequent length of follow-up. These results thus indicate no association between the two factors. (8 refs)

78-2153 **Aspiration Curettage for Asymptomatic Patients Receiving Estrogen.** (Eng) Buchman, M. (117 E. 72 St., Cornell Medical Center, New York, NY, 10021); Kramer, E.; Feldman, G. B. *Obstet Gynecol* 51(3): 9-341; 1978.

The value of endometrial aspiration curettage in normal patients receiving exogenous estrogens was evaluated based on 17 curettages of 208 women aged 40-70 yr. The mean duration of estrogen therapy was 7.7 yr. A total of 132 curettages were performed on women receiving progestagens during the last 5 days of their estrogen cycle, and 117 were performed on women with a predisposition to endometrial malignancy. Normal endometrium, ranging from focal hyperplasia to Grade 1 adenocarcinoma, was found in 67 samples. Of these, 33 were from patients with a predisposed risk and 33 were from patients treated with estrogens alone. Two curettages showed atypical adenomatous hyperplasia, three Grade 1 adenocarcinomas, and one a Grade 2 adenocarcinoma. Two of these six patients were obese, hypertensive, nulliparous, or diabetic; four were taking progestagens. Although these patients were significantly older than patients with benign endometrial conditions, the mean duration of their estrogen treatment was not significantly different. (7 refs)

78-2154 **Activation of Growth of Dormant Autonomous Lymphoma Cells Following Pulses of Estrogen Acting Through the Pituitary Gland in Nb Rats (Meeting Abstract).** (Eng) Noble, R. L. (Cancer Res. Centre, Univ. of British Columbia, Vancouver, B.C. V6T 1W5, Canada). *Proc Am Assoc Cancer Res* 19: 216; 1978. (no refs)

78-2155 **Ethinyl Estradiol May Lead to Malignancy (2 Letters to Editor).** (Eng) Eichner, E. (Severance Medical Arts Building, 5 Severance Circle, Cleveland Heights, OH, 44118); Yasuda, Y.; Kihara, T.; Takeda, T. *Am J Obstet Gynecol* 130(4): 506-508; 1978.

A previous conclusion that ethinyl estradiol (EE) leads to malignant involvement of the uterine endometrium and vaginal epithelium in humans and mice is criticized because only hyperplasia was actually demonstrated in the mice. In a rebuttal, it is maintained that prenatal EE induces ovary-independent hyperplasia and endometriosis in mice; older mice are being examined for malignant changes. (1 ref)

78-2156 **Effect of Ethynodiol Diacetate with Ethinyl Estradiol on the Mammary Glands of Rhesus Monkeys: A Preliminary Report.** (Eng) Drill, V. A. (Dept. Pharmacology, Coll. Medicine, Univ. Illinois Medical Center, Chicago, IL, 60680); Golway, P. L. *J Natl Cancer Inst* 60(5): 1169-1170; 1978.

An interim (5-yr) report is given of a 10-yr study of the effects of the oral contraceptive Demulen on the occurrence of mammary gland cancer in 48 female rhesus monkeys. Demulen is a combination of ethynodiol diacetate (ED) + ethinyl estradiol (EE). The monkeys were divided into three groups of 16 animals each and treated with a low (0.02 mg/kg ED + 0.001 mg/kg EE), medium (0.2 mg/kg ED + 0.01 mg/kg EE), or high (1.0 mg/kg ED + 0.05 mg/kg EE) dose level. Based on body wt, the experimental doses for the monkeys were 1, 10, and 50 times the dose for a 50-kg woman. Demulen was given po, once daily, 7 days/wk for 3 consecutive weeks. This cyclic administration for 21 days of each 28-day cycle was continued for the 5 yr of the study to date. An additional 16 control animals received a placebo. The treatments did not induce palpable breast nodules, and there were no deaths from mammary gland cancer. (3 refs)

78-2157 **Structural Modifications in Contraceptive Steroids Altering Their Metabolism and Toxicity.** (Eng) Bolt, H. M. (Institut für Toxikologie, Universität Tübingen, Wilhelmstrasse 56, D-7400 Tübingen, W. Germany). *Arch Toxicol (Berl)* 39(1/2): 13-19; 1977.

The activation of contraceptive steroids to compounds with potentially toxic effects was investigated. Norethisterone and, to a lesser extent, d-norgestrel were metabolically activated by rat liver microsomal enzymes to intermediates capable of binding irreversibly to proteins. This microsomal activation in vitro depended on the presence of NADPH and was inhibited by glutathione. Irreversible binding of metabolites of progesterone, nortestosterone acetate, and cyproterone acetate was very low compared with that of norethisterone.



terone metabolites. Norethisterone-4 $\beta$ ,5 $\beta$ -epoxide, a microsomal metabolite of norethisterone, bound non-enzymatically to albumin at a rate of 380 picomoles (pmol)/mg albumin/hr. The corresponding rate for norgestrel-4 $\beta$ ,5 $\beta$ -epoxide was 42 pmol/mg albumin/hr, indicating a considerably lower reactivity. The non-sulfhydryl proteins, concanavalin A and bovine  $\gamma$ -globulin, did not react with either norethisterone epoxide or norgestrel epoxide. DNA and RNA also showed no binding reaction. Hepatomas have been observed in rats on long-term administration of large doses (120 times the human contraceptive dose) of norethisterone and its isomer norethynodrel. Norgestrel had no such effect at up to 200-400 times the human contraceptive dose. This may be partly due to the contraceptive dose of norgestrel, which is much lower than that of norethisterone, or to the fact that norgestrel is much less metabolically activated to metabolites that bind to proteins. (19 refs)

- 78-2158 Urinary Steroid Profiles in Normal Women and in Patients with Breast Cancer in Britain and Japan: Relation to Thyroid Function.** (Eng) Thomas, B. S. (Dept. Clinical Endocrinology, Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London, WC2A 3PX, England); Bulbrook, R. D.; Hayward, J. L.; Kumaoka, S.; Takatani, O.; Abe, O.; Utsunomiya, J. *Eur J Cancer* 13(11): 1287-1292; 1977.

Steroid profiles of urinary 17-oxosteroids, pregnanediol and pregnanetriol were studied by gas-liquid chromatography in normal Japanese and British women and in women of both races with breast cancer. The results showed that pre- and postmenopausal Japanese women excreted significantly less etiocholanolone, 11-oxoetiocholanolone, and 11-hydroxyetiocholanolone than their British counterparts. Androsterone was significantly less in premenopausal and pregnanetriol in postmenopausal women, respectively. However, the androsterone (5 $\alpha$ ):etiocholanolone (5 $\beta$ ) ratio was significantly lower in Japanese cancer patients than in normal Japanese women. In premenopausal British breast cancer patients, this 5 $\alpha$ :5 $\beta$  ratio was higher than in normal British controls. A comparison of blood plasma thyroid-stimulating hormone levels with the urinary androsterone:etiocholanolone ratios gave a significantly negative correlation in both the Japanese normal and cancer subjects. No agreement was found in a similar comparison in British women. A diminished thyroid function may be a predisposing factor to breast cancer in Japanese women. (19 refs.)

- 78-2159 Plasma Thyroid-stimulating Hormone and Thyroxine Concentrations in Breast Cancer.** (Eng) Rose, D. P. (Div. Clinical Oncology, Univ. Wisconsin

Hosp., Madison, WI, 53706); Davis, T. E. *Cancer* 41(2): 669; 1978.

The association between hypothyroidism and breast cancer was investigated in 74 early breast cancer patients, 53 advanced breast cancer patients, 77 patients with cancer at other organs, and 67 healthy women of similar age, measuring their plasma thyroid-stimulating hormone (TSH) and thyroxine levels. The mean plasma TSH levels were higher in all breast cancer patients than in the other two groups but the difference was only statistically significant in patients with advanced disease. A total of 12% of the early and 10% of the advanced breast cancer patients had elevated plasma TSH concentrations, compared to 1% of the other cancer patients and 3% of the controls. Four breast cancer patients with plasma TSH levels > 85  $\mu$ IU/ml had subnormal plasma thyroxine levels. Five of 29 early breast cancer patients had excessive plasma TSH responses to thyrotropin-releasing hormone. Thus, although a minority of breast cancer patients may have a compensated impairment of thyroid function, it is unlikely that this could be a significant factor in the etiology of the disease. (22 refs)

- 78-2160 Effect of Neonatal Administration of Sex Hormones on 7,12-Dimethylbenz[a]anthracene-induced Auditory Sebaceous Gland Tumor in Female Sprague-Dawley Rats.** (Eng) Yoshida, H. (First Dept. Pathology, Sch. Med. Ehime Univ., Shizukawa, Shigenobu-cho, Onsen, Ehime-ken 791-02, Japan); Fukunishi, R. *Gann* 68(6): 852; 1977.

The effect of neonatal sex administration on sex hormone-induced auditory sebaceous gland tumorigenesis was studied in female Sprague-Dawley rats. Newborn rats were divided into three groups: Group 1 received no treatment, Groups 2, 3, and 4 were given 1.0 mg testosterone propionate, 100  $\mu$ g estradiol, or 1.0 mg progesterone, respectively, at 2 days of age. At 50 days, all groups received 20 mg 7,12-dimethylbenz(a)anthracene by gastric intubation. The rats were observed for 250 days. Keratinizing epidermal carcinomas of the auditory sebaceous glands were found in 1 animal in Groups 1, 2, and 3. Eight tumors were found in eight rats in Group 2, compared with one tumor in 1 rat in Group 1 and one in Group 3; this difference was significant. Of the rats in Groups 2 or 3 had corpora lutea in their ovaries, while rats in Groups 1 and 4 had normal ovaries. Thus, testosterone propionate increases the incidence of auditory sebaceous gland tumors, and female sex hormone alterations have a significant effect on tumorigenesis. (9 refs)

- 78-2161 Selective Reduction in the Binding of Epidermal Growth Factor-Urogastrone by Chemically**  
**Transformed Syrian Hamster Embryonic Fibroblasts**



(Abstract). (Eng) Hollenberg, M. D. (Div. Clinical Pharmacology, Sch. Medicine, Johns Hopkins Univ., Baltimore, D, 21205); Barrett, J. C. *Proc Am Assoc Cancer Res* 19: 70; 78. (1 ref)

78-2162 **Carcinogenicity Study of Rifampicin in Mice and Rats.** (Eng) Della Porta, G. (Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan, Italy); Canal, J. R.; Rossi, L. *Toxicol Appl Pharmacol* 43(2): 293-302; 78.

Rifampicin was given, in the drinking water, to C3Hf and BALB/c mice at three dose levels (0.01%, 0.03%, and 0.06%) for 60 wk beginning at 8 wk of age and to Wistar rats (two dose levels (0.03% and 0.06%) for 104 wk beginning at 6 wk of age. The C3Hf and BALB/c mice and the rats were observed until 114, 120, and 144 wk of age, respectively. The treatment had no adverse effects on body growth or survival. In all the control and treated groups of mice and rats, a considerable number of animals developed tumors. Statistically significant excesses of hepatomas were found in C3Hf male mice treated with rifampicin and in one control group BALB/c male mice. An excess of Harderian gland tumors was observed in another control group of BALB/c male mice treated with sodium ascorbate. No significant differences in tumor incidence were found among the rat groups. The significance of the rifampicin-associated hepatomas in the C3Hf male mice is not clear, but it is conceivable that rifampicin, rather than acting directly as a liver carcinogen, somehow modified the hormonal balance, thereby increasing the susceptibility of these mice to the development of spontaneous hepatomas. This interpretation is supported by the absence of any increase in hepatoma incidence in similarly treated BALB/c mice and Wistar rats of both sexes. (22 refs)

78-2163 **Photomirex: Synthesis and Assessment of Acute Toxicity, Tissue Distribution, and Mutagenicity.** (Eng) Hallett, D. J. (Dept. Fisheries and Environment, Toxic Chemicals Div., Canadian Wildlife Service, Natl. Wildlife Res. Centre, Ottawa, Ontario, K1A 0E7, Canada); Mera, K. S.; Stoltz, D. R.; Chu, I.; Villeneuve, D. C.; Trill, G. *J Agric Food Chem* 26(2): 388-391; 1978.

The toxicity of photomirex (8-monohydromirex) was investigated in Wistar rats given single po doses of 0, 50, 100, 150, 200 mg/kg. The highest dose caused an 80% mortality in males and a 40% mortality in females. Surviving animals of both dose groups had dose-dependent mottled and congested lungs and kidneys; hemorrhagic ovaries were noted in females at doses > 100 mg/kg. Mirex, photomirex, and ketone were not mutagenic in the Ames assay. (26 refs)

78-2164 **Mutagenicity Studies with Praziquantel, a New Anthelmintic Drug, in Mammalian Systems.** (Eng) Machemer, L. (Bayer AG, Pharma-Forschung, Institut für Toxikologie, Postfach 101709, D-5600 Wuppertal-Elberfeld, W. Germany); Lorke, D. *Arch Toxicol (Berl)* 39(3): 187-197; 1978.

Various in vivo tests were performed on the anthelmintic drug praziquantel to determine its mutagenic properties. The tests included the following: (1) dominant lethal tests on male NMRI mice, 12 mating periods of 4 days each, after 1,200 mg/kg po; (2) dominant lethal tests with female NMRI mice, 1,200 mg/kg po during pre-estrus; (3) micronucleus tests on male and female NMRI mice, two doses of 300 or 600 mg/kg po at 24-hr intervals, with examination of the marrow 6 hr after the second dose; and (4) spermatogonia tests on Chinese hamsters with two doses of 600 mg/kg po at 24-hr intervals, with spermatogonia preparation 48 hr after the second dose. The 1,200-mg/kg dose corresponded to 50% of the po LD50 in the mouse and approx 40 times the therapeutic dose. Praziquantel was not mutagenic in any of the test systems. (27 refs)

78-2165 **Carcinogenic and Other Adverse Effects of Procarbazine in Non-Human Primates (Meeting Abstract).** (Eng) Sieber, S. M. (NIH, Bethesda, MD, 20014); Correa, P.; Dalgard, D. W.; Adamson, R. H. *Proc Am Assoc Cancer Res* 19: 154; 1978. (no refs)

See also:

- \*(Rev.): 78-1801, 78-1802, 78-1803, 78-1804, 78-1805, 78-1806, 78-1807, 78-1808, 78-1812, 78-1813, 78-1814, 78-1826, 78-1827, 78-1828, 78-1829, 78-1830, 78-1834, 78-1840, 78-1842, 78-1845, 78-1846, 78-1849, 78-1850, 78-1851, 78-1852, 78-1853, 78-1854, 78-1855, 78-1857, 78-1859.
- \*(Phys.): 78-2166, 78-2167, 78-2173, 78-2174, 78-2183.
- \*(Viral): 78-2201, 78-2209, 78-2231, 78-2248, 78-2291.
- \*(Immun.): 78-2321, 78-2322.
- \*(Path.): 78-2337, 78-2338, 78-2351.
- \*(Epid.-Biom.): 78-2361, 78-2362, 78-2364, 78-2365, 78-2366, 78-2373, 78-2374, 78-2387.



## PHYSICAL CARCINOGENESIS

### 78-2166 5-S-Cysteinyl-dopa Excretion after Treatment with 8-Methoxypsoralen and UVA Light. (Eng)

Agrup, G. (Dept. Dermatology, Lasarettet, S-221 85 Lund, Sweden); Hansson, C.; Rorsman, H.; Rosengren, A. M.; Rosengren, E.; Tegner, E. *J Invest Dermatol* 70(1): 25-26; 1978.

Five Caucasians with psoriasis were given 30-40 mg 8-methoxypsoralen 2 hr before exposure to 0.5-9.0 joules/cm<sup>2</sup> UV-A light. The urinary concentration of the melanocytic metabolite 5-S-cysteinyl-dopa increased after 2 days of treatment and reached a max after 1-2 wk; increased pigmentation was noted after 1 wk of treatment. By 10 wk, the psoriasis lesions had cleared up in all patients. (6 refs.)

### 78-2167 Carcinogenic Effects of Photochemotherapy in Psoriasis. (Ger) Wolff, K. (Klinik für Dermatologie und Syphilidologie, Universität Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria). *Hautarzt* 28(11): 625; 1977.

An increased sister chromatid exchange rate was found in vitro in lymphocytes from psoriatic patients treated with UV radiation and 8-methoxypsoralen, but no such increase was seen in vivo. (16 refs.)

### 78-2168 Sister Chromatid Exchanges in Lymphocytes of Psoriatics after Treatment with 8-Methoxypsoralen and Long Wave Ultraviolet Radiation. (Eng) Mourelatos, D. (Cytogenetics Lab., Dept. Pathology, Univ. Dundee, Dundee, Scotland); Faed, M. J.; Gould, P. W.; Johnson, B. E.; Frain-Bell, W. *Br J Dermatol* 97(6): 649-654; 1977.

The effect of 8-methoxypsoralen (8-MOP) and long wave UV radiation (UVA; 320-400 nanometers) on the sister chromatid exchange (SCE) rate in lymphocytes of psoriasis patients was determined. When 8-MOP (0.8 mg/kg po) was taken 2 hr before radiation (2-3 joules/cm<sup>2</sup> over 20-30 min), no increase in the SCE rate was observed compared to the rate measured before irradiation. However, if cells obtained after 8-MOP ingestion, but before in vivo UVA exposure, were irradiated in vitro, a significant increase in SCE's was noted. To determine if radiation alone could increase the SCE rate, cells from patients who had never received 8-MOP treatment underwent UVA treatment in vitro. There was no significant increase in posttreatment SCE's compared to pretreatment

SCE's. Cells from two untreated patients were treated in vitro with 4 µg/ml 8-MOP and 30 min UVA exposure; the SCE rate increased approx three times over the control level. The increase was related to the presence of 8-MOP in the peripheral circulation. (16 refs)

### 78-2169 Effect of Ultraviolet Light and HSV Infection upon Mouse Lips (Meeting Abstract). (E) Burns, J. (Medical Coll. Virginia/VCU, Richmond, VA); Murray, B. *J Dent Res* 57(A): 147; 1978. (no refs)

### 78-2170 Growth Patterns of Ultraviolet Light-induced Fibrosarcomas in Subcutaneous, Peritoneal, and Vascular Compartments of Syngeneic Recipients. (E) Lill, P. H. (Basic Res. Program, NCI, Frederick Cancer Center, Frederick, MD, 21501); Kripke, M. L. *Transplantation* 25(2): 86-87; 1978.

Three cell lines (1316, 2343, and 2237) were derived from fibrosarcomas produced by chronic UV irradiation of C3H/HeN(MTV-) mice, and their growth patterns were determined following sc, ip, or iv injection into syngeneic recipients. Sc injection of 10<sup>5</sup>-10<sup>7</sup> cells in normal C3H/HeN mice resulted in no tumors in all mice receiving 1316 cells, no tumors in mice receiving the lowest dose of 2343 cells, and tumors in some mice at all doses of 2237 cells. Injection of 10<sup>5</sup> cells into athymic mice resulted in 100% tumor incidence with all three lines. A dose of 10<sup>6</sup> cells from all lines was then injected sc, ip, or iv in syngeneic mice. No tumors developed following injection of 1316 cells by any route. Injection of 2237 cells resulted in tumors in 10/10 mice by each route. Sc injection of 2343 cells resulted in 7/10 tumors, ip injection 5/10 tumors, and iv injection 3/10 tumors. The route of tumor injection did not affect the percentage of tumor-bearing mice, but it did affect survival time. With 2343 and 2237 cells, animals inoculated ip died first, those inoculated sc were to die, and those inoculated iv died last. It is suggested that a balance between the host's ability to respond to the tumor and the tumor's ability to proliferate determines the outcome of a particular host-tumor interaction. (8 refs)

### 78-2171 Heterogeneity of Metastatic Potential in Fibrosarcomas from a Murine UV-induced Fibrosarcoma (Meeting Abstract). (Eng) Kripke, M. L. (Basic Res. Program, NCI, Frederick Cancer Center, Frederick, MD, 21501)



ram, NCI-Frederick Cancer Res. Center, Frederick, MD, 1501); Fidler, I. J.; Gruys, E. *Proc Am Assoc Cancer Res* 19: 13; 1978. (no refs)

**8-2172 Deficient Recovery from Potentially Lethal Radiation Damage in Ataxia Telangiectasia and Xeroderma Pigmentosum.** (Eng) Weichselbaum, R. R. (Lab. Radiobiology, Dept. Physiology, Harvard Univ., Sch. Public Health, Boston, MA 02115); Nove, J.; Little, J. B. *Nature* 71(5642): 261-262; 1978.

The capacity of skin fibroblast cell strains derived from patients with xeroderma pigmentosum (XP) and ataxia telangiectasia (AT) to perform potentially lethal damage repair (PLDR) following either UV or x-irradiation was examined, and the results were compared with those of a normal diploid fibroblast cell strain. PLDR refers to the enhancement in cell survival that occurs when mammalian cells are maintained in a density-inhibited state for a short time after the radiation exposure. The XP skin fibroblasts showed no PLDR following UV irradiation, and the AT skin fibroblasts were specifically deficient in PLDR following x-ray irradiation. An XP variant cell strain was able to carry out PLDR following UV light irradiation. Thus, cells deficient in molecular repair following x-ray (AT) or UV (XP) exposure are similarly defective in PLDR. The results suggest that PLDR as a general phenomenon in density-inhibited cells reflects molecular repair processes, which in turn are reflected by an increase in survival. The fact that XP variant cells could perform PLDR suggests that UV-induced PLDR may specifically reflect the excision repair pathway. Deficiencies in this type of repair may contribute to the general predisposition to malignancies in AT and XP patients. (11 refs.)

**8-2173 Defective and Enhanced Postreplication Repair in Classical and Variant Xeroderma Pigmentosum Cells Treated with N-Acetoxy-2-acetylaminofluorene.** (Eng) D'Ambrosio, M. (Dept. Radiology, N212 Univ. Hosp., Ohio State Univ., Columbus, OH, 43210); Setlow, R. B. *Cancer Res* 38(4): 1147-1153; 1978.

Xeroderma pigmentosum (XP) cells proficient in the excision repair of pyrimidine dimers (XP variants) were found to be deficient in the excision repair of N-2-acetoxyacetylaminofluorene (AAAF)-induced lesions in their DNA, as assayed by the photolysis of 5-bromodeoxyuridine incorporated during repair. However, the time in which the small segments of newly synthesized DNA, made immediately after treatment of the cells with AAAF, were joined together to form DNA of parental size postreplication repair was long in the XP variant and classical cells. Although increasing doses of AAAF increased the rate for making daughter DNA of parental size for variant and classical XP cells, AAAF did not appear to affect this

process in normal human cells. Treatment of variant and classical XP cells with a relatively small dose (2.5  $\mu$ M) of AAAF or 2.5 joules/m<sup>2</sup> of UV radiation several hours before a two- to threefold-larger dose decreased the time for the pulse-labeled DNA to appear as parental size. These results, combined with those in the literature, suggest that in normal, classical, and variant XP cells, postreplication repair plays a role in mutagenesis and appears to be error-prone, but excision repair appears to be error-free. (37 refs)

**78-2174 Enhancement of X-Ray Transformation by 12-O-Tetradecanoyl-phorbol-13-acetate in a Cloned Line of C3H Mouse Embryo Cells.** (Eng) Kennedy, A. R. (Lab. Radiobiology, Dept. Physiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA 02115); Mondal, S.; Heidelberger, C.; Little, J. B. *Cancer Res* 38(2): 439-443; 1978.

A study was undertaken to determine whether a promoting agent could enhance x-ray transformation in vitro, as had been shown previously for UV radiation and chemical carcinogens. In studies with a mouse embryo-derived cell line [C3H/10T(1/2) clone 8], there were clear interactive effects between x-radiation and the promoting agent, 12-O-tetradecanoylphorbol-13-acetate (TPA). These effects were particularly marked when exposure to minimally transforming x-ray doses (50 or 100 rads) was followed by TPA treatment immediately or 48 or 96 hr later. However, TPA was considerably less efficient at enhancing x-radiation transformation than UV light- or chemical carcinogen-induced transformation. This may be explained by the fundamental differences in the mechanism of action of x-rays, UV light, and chemical carcinogens. Possible mechanisms that may account for the effect of TPA are as follows: (1) TPA may reduce the number of post-irradiation cell divisions required for the expression of transformation; and (2) at high cell densities the growth of transformed cells induced by x-rays might be suppressed, and TPA may reverse the suppression. (31 refs.)

**78-2175 A Search for an Effect of Ultrasound Alone and in Combination with X Rays on Chromosomes In Vivo.** (Eng) Harkanyi, Z. (Radiological Clinic, Semmelweis Medical Univ., 1082 Budapest, Ulloi ut 78/a, Hungary); Szollar, J.; Vigvari, Z. *Br J Radiol* 51(601): 46-49; 1978.

Male CBA/H-T<sub>6</sub>J mice were exposed to varying doses of ultrasound and/or x-rays to determine whether the former has any effect on chromosomal aberrations in vivo. Rats were exposed to either (I) 0.1, 0.5, or 1.0 watts/cm<sup>2</sup> ultrasound, (II) 50 R whole-body x-radiation, or (III) 0.1 or 1.0 watts/cm<sup>2</sup> ultrasound followed 2 hr later by 50 R x-radiation. Mice were killed 24 hr after treatment, and the bone marrow was examined. Structural aberrations



in all Group I rats showed no significant increase compared with untreated controls. An increase in intensity did not lead to a proportionate increase in structural aberrations. However, the number of aberrations in Group III was significantly higher than the number in Group I or the controls. Furthermore, there was no significant difference in aberrations between Groups II and III. These findings indicate that low ultrasound doses do not influence the chromosome damage by x-rays. (22 refs)

**78-2176 Augmenting Influence of Whole Body X-Irradiation on Natural Lymphocyte Cytotoxicity (Meeting Abstract).** (Eng) Moroson, H. (New York Medical Coll., New York, NY, 10029); Schechter, M. *Proc Am Assoc Cancer Res* 19: 45; 1978. (no refs)

**78-2177 Tumorigenic Effects of Irradiation in Neonatally Thymectomized Germfree Mice (Meeting Abstract).** (Eng) Anderson, R. E. (Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131); Pogue, L. E. *Fed Proc* 37(3): 412; 1978. (no refs)

**78-2178 Preleukemic Change in the Bone Marrow of Whole-Body Irradiated RFM/Up Mice.** (Eng) Ludwig, F. C. (Dept. Pathology, Coll. Medicine, Univ. California, Irvine, CA 92717); Smoke, M. E.; Schug, W. G.; Bostick, W. L. *Res Exp Med* 171(3): 277-287; 1977.

Preleukemic changes in blood-forming tissues of mice after recovery from acute radiation injury were investigated. Radiation exposure enhanced the incidence of leukemias, which were classified as thymic and extrathymic lymphomas and myeloid leukemia. Spleen shielding, splenectomy, and re-irradiation followed by bone marrow substitution reduced leukemia incidence and modified the nonmalignant late effects of radiation. Leukemia incidence was negatively correlated with the myeloid index (the percentage of mature cells in the entire series), regardless of the absolute cell numbers involved. It is postulated, therefore, that the removal of a controlling influence, exerted by the mature cells over their immature precursors, enhances proneness to leukemia. The relevant characteristic of the target cell, the ability to react with a latent virus, is likely to be conferred (or removed) by factors outside the cell. (22 refs.)

**78-2179 Thyroid Neoplasms after Radiation Therapy for Adolescent Acne Vulgaris.** (Eng) Paloyan, E. (Dept. Surgery, Loyola Univ. Stritch Sch. Medicine, P.O.

Box 5, Hines, IL 60141); Lawrence, A. M. *Arch Dermatol* 114(1): 53-55; 1978.

The possible hazard of thyroid cancer after radiation therapy for acne vulgaris is reported, and the findings in several new cases are described. Twelve of 20 thyroidectomy patients who had a history of radiation therapy for acne vulgaris in adolescence had a carcinoma; among the other 8 patients, the principal pathological changes consisted of follicular adenoma, colloid nodules, and chronic Hashimoto's thyroiditis. Two of the carcinoma patients were men and 10 were women. The interval between exposure to radiation and thyroidectomy was 9-41 yr in the carcinoma patients. Ten of the 12 patients had a follicular component in their tumor. Four patients had regional lymph node metastases, but none had distant metastases. The association of thyroid neoplasms and a prior history of radiation for acne vulgaris may be coincidental, but the 60% incidence of carcinoma in this group is comparable to the incidence reported in patients who received radiation therapy for tonsillitis. The incidence of follicular carcinoma is also similar. Thyroidectomy should be considered in patients with a history of radiation exposure for the treatment of acne vulgaris when thyroid nodules appear. Controlled retrospective studies on a large scale in irradiated and nonirradiated acne patients are needed to clarify the potential carcinogenicity of proper radiation therapy techniques for acne. (12 refs.)

**78-2180 Radiation-induced Parathyroid Tumors Following Head and Neck Radiation in Childhood (Meeting Abstract).** (Eng) Okerlund, M. D. (Nuclear Medicine Section, Univ. California Medical Center, San Francisco, CA); Beckmann, A.; Galante, M.; Hunt, T. *Clin Res* 26(2): 191A; 1978. (no refs)

**78-2181 Age-related Differences in Thyroidal Dose from Environmental Radioiodines (Meeting Abstract).** (Eng) Book, S. A. (Radiology Lab., Sch. Veterinary Medicine, Univ. California, Davis, CA, 95616). *Health Phys* 33(6): 679, 681; 1977. (no refs)

**78-2182 Cell Migration Following Irradiation of the Skin in Mice. Effect of Shielding Minute Areas (Eng) Devik, F.** (Medical Section, State Inst. Radiation Hygiene, Univ. Oslo, Oslo, Norway). *Acta Radiol [Ther]* (Stockh) 16(3): 257-265; 1977.

An attempt was made to determine the cells responsible for the border hyperplasia that follows the irradiation of female hairless (rh, rh) mice. The mice were anesthetized, and dorsal skin flaps were exposed to 15 kilovolts of roentgen radiation. Thin metal wires were stretched across the field to shield narrow strips 1-3 mm apart. At eight different intervals,



days, and following an injection of Colcemid (0.15  $\mu$ g/kg), the number and location of mitoses in the epidermis were recorded. In 22 mice exposed to 10,800 R without any wire shielding, normal mitoses or clusters of mitoses were not observed up to 6 days after irradiation. A smaller series exposed to 2,700 R had similar results, excepting that the mitoses had a longer maturation time of 1.4 days. Mitoses were located in the basal epidermis, and the epithelium above the mitoses was hyperplastic; there was little or no evidence of decreased numbers of cells in the epithelium where the mitoses occurred. The regeneration appeared to be due to the migration of cells from shielded areas, with the rate for the first 6 days being 1/6 mm/day. Cell migration occurs in the basal membrane before apparent cell loss in the superficial layers. (10 refs.)

**183 Photodynamic Action of Fluorescein Dyes in Transforming DNA in Bacteria.** (Eng) Yoshikawa, K. (Dept. Microbiology, Natl. Inst. Hygiene Sciences, Kamiyoga 1-18-1, Setagaya-ku, Japan); Kurata, H.; Iwahara, S.; Kada, T. *Int J Radiat Res* 56(3): 359-362; 1978.

The photodynamic action of various fluorescein dyes was investigated using *Bacillus subtilis* in the rec-assay. In the rec-assay, most fluorescein dyes did not damage DNA without light, but some damage was noted under light, especially with erythrosine, phloxine B, and rose bengal. The effect was pH dependent and was greater at pH 7.2 than 7.0. All halogenated fluorescein dyes inactivated transforming DNA from *B. subtilis* 457 H more under light than in the dark. However, neither fluorescein nor its sodium salt inactivated the DNA with or without light. Under light conditions, the order of inactivation was in the following order: 2,7-dichlorofluorescein < 4,5-dichlorofluorescein = 12,13,14,15-tetrachlorofluorescein < 2,7-dibromofluorescein < 4,5-dibromofluorescein < erythrosine < eosine Y < phloxine B < rose bengal. Since the photodynamic action of fluorescein dyes in producing DNA damage and the in vitro inactivation of transforming DNA might be caused by photosensitized oxygenation, all halogenated fluorescein dyes could be considered mutagenic under light. (7 refs)

**184 Early Effects of  $^{239}\text{Pu}(\text{NO}_3)_4$  Inhalation in Dogs (Meeting Abstract).** (Eng) Dagle, G. E. (Dept. Biology, Battelle Pacific Northwest Lab., Richland, WA 99352); Cannon, W. C.; Ragan, H. A.; Watson, C. R. *Health Phys* 33(6): 666; 1977.

Male dogs were exposed once to aerosols of  $^{239}\text{Pu}(\text{NO}_3)_4$  at group average estimated retained levels of 5400 nCi (nCi), 2300 nCi, 310 nCi, 59 nCi, and approx 2 nCi. The  $^{239}\text{Pu}(\text{NO}_3)_4$  was nebulized in 0.27 N  $\text{HNO}_3$

for nose only exposures, with the higher exposure level having larger median diameter aerosols since the higher exposure levels required greater aerosol and solution concentrations. Ultrafiltration and valence determinations on the solution showed no appreciable polymerization or disproportionation at the concentrations used. Dogs from selected dosage levels have been sacrificed at intervals to 3 months postexposure for examination of pathology and plutonium distribution. A significant lymphopenia was present in the two highest dosage levels at one month postexposure. At four months postexposure there was a reduction in total leukocytes, neutrophils, and lymphocytes at the two highest dosage levels. The early changes present after inhalation of this relatively soluble form of plutonium will be compared with changes observed following inhalation of insoluble plutonium. (no refs)

**78-2185 The In Vivo Solubility of Plutonium-239 Dioxide in the Rat Lung.** (Eng) Smith, H. (Natl. Radiological Protection Board, Harwell, Didcot, Oxfordshire, England); Stradling, G. N.; Loveless, B. W.; Ham, G. J. *Health Phys* 33(6): 539-551; 1977.

The effect of particle size on the movement and solubility of plutonium dioxide ( $^{239}\text{PuO}_2$ ) was investigated in male Sprague-Dawley rats after they were administered fractionated suspensions of a polydisperse aerosol by pulmonary intubation or iv injection. Particles  $>0.025 \mu\text{m}$  remained in the lungs after intubation or were deposited in the liver after iv injection. Particles of  $0.001 \mu\text{m}$  diameter moved rapidly from the lungs to the blood, where they underwent a rapid reaction. In vitro and in vivo experiments suggest that this reaction involves citrate ions and that an unidentified low-molecular-weight chemical species of  $^{239}\text{Pu}$  with citrate is formed. This intermediate species then forms  $^{239}\text{Pu}$  citrate and, eventually,  $^{239}\text{Pu}$  transferrin. The intermediate species is the predominant form of  $^{239}\text{Pu}$  in urine within 20 min of an iv injection of  $0.001 \mu\text{m}$   $^{239}\text{PuO}_2$  particles, but it is subsequently transformed to  $^{239}\text{Pu}$  citrate. IV injection of the calcium salt of diethylenetriaminepentaacetic acid ( $\text{Na}_3\text{CaDTPA}$ ) effectively removed the  $0.001 \mu\text{m}$  component of a polydisperse aerosol of  $^{239}\text{PuO}_2$  if given within 1 hr of the Pu-particle injection. These results indicate that a polydisperse aerosol containing a high  $0.001 \mu\text{m}$ -particle fraction will behave differently from what had been predicted by a previous model, which defined  $^{239}\text{PuO}_2$  as an insoluble compound. Any attempt to estimate the body content (excluding lungs) of  $^{239}\text{Pu}$  by applying a fixed factor to cumulative urinary excretion will require adjustments to account for the enhanced excretion of  $^{239}\text{Pu}$  in the early period after an intake of  $0.001 \mu\text{m}$  particles. (23 refs)

**78-2186 Effects of Mass of Injected Plutonium on its Distribution and Retention in Mouse Tissues**



(Meeting Abstract). (Eng) Guilmette, R. A. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439); Lindenbaum, A.; Moretti, E.; Russell, J. J. *Health Phys* 33(6): 667-668; 1977. (no refs)

**78-2187 Solvent Extraction Method for Determination of Plutonium in Soft Tissue.** (Eng) Singh, N. P. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Ibrahim, S. A.; Cohen, N.; Wrenn, M. E. *Anal Chem* 50(2): 357-360; 1978.

A new method for the determination of plutonium levels in soft tissue is described. Using this method, recovery ranged from 49% to 85%, with a mean of 61%. Pu content in beef liver was 100 times lower than that in human liver. It is suggested that Pu concentrations in mammals increase with age. (18 refs)

**78-2188 Deposition, Retention and Excretion in the Beagle Dog of Inhaled Mixed Plutonium and Uranium Oxides as Processed in a Fuel Fabrication Facility (Meeting Abstract).** (Eng) Eidson, A. F. (Inhalation Toxicology Res. Inst., P. O. Box 5890, Albuquerque, NM, 87115); Mewhinney, J. A.; Stanley, J. A.; Mo, T. *Health Phys* 33(6): 667; 1977. (no refs)

**78-2189 Uranium: Health Risks from a Nuclear Power Industry.** (Eng) Kerr, C. (No affiliation given). *Med J Aust* 2(18): 283-286; 1977.

Every stage of uranium handling in the nuclear power industry presents actual and potential hazards to human health. Danger begins in the mining operation, where the decay product radon can cause lung cancer. Milling results in decay products that produce harmful radiation for up to thousands of years. Methods for the reprocessing of spent fuel must be developed to protect people from the harmful effects of long-lived radioactive wastes. (21 refs)

**78-2190 The Beta Dose to Critical Human Tumor Sites from Krypton-85.** (Eng) Harley, N. H. (New York Univ. Medical Center, Inst. Environmental Medicine, 550 First Ave., New York, NY, 10016); Pasternack, B. S. *Health Phys* 33(6): 567-575; 1977.

Beta doses from krypton-85 to cells critical to human tumor formation (hemopoietic stem cells, osteoprogenitor cells on bone surfaces, and basal cells in bronchial epithelium) were estimated.  $^{85}\text{Kr}$  is soluble in body tissues, particularly fat, and is capable of delivering a beta dose to all of these cell types. The annual absorbed beta dose rates for the current global

$^{85}\text{Kr}$  level of 15 picocuries (pCi)/ $\text{m}^3$  are  $1 \times 10^{-5}$  mrad for on bone surfaces,  $2 \times 10^{-5}$  mrad for hemopoietic stem cells, and  $3 \times 10^{-4}$  mrad for basal cells in bronchial epithelium. In comparison, the annual alpha dose rates from the average concentration of 100 pCi/m of the naturally occurring gas radon and its daughter products are  $2.5 \times 10^{-2}$ ,  $3.6 \times 10^{-2}$ , and 1 mrad, respectively, to the same three cell types. The health effects of the predicted  $^{85}\text{Kr}$  exposure cannot be evaluated directly, but they should be considerably less than those estimated by comparing exposure to  $^{222}\text{Rn}$ , even in the year 2000, when the level of  $^{85}\text{Kr}$  in the atmosphere is expected to be 1 pCi/ $\text{m}^3$ . (25 refs)

**78-2191 The Effect of Temperature on the Metabolism of Strontium-85 in Two Amphibian Species (*Taricha granulosa* and *Rana pipiens*) (Meeting Abstract).** (Eng) Willis, D. L. (General Science Dept., Oregon State Univ., Corvallis, OR, 97331); Valett, B. B.; Hickerson, R. *Health Phys* 33(6): 684; 1977. (no refs)

**78-2192 Strontium-90 and Caesium-137 Contents in Human Teeth.** (Eng) Glowiak, B. J. (Environmental Protection Engineering Inst., Technical Univ. Wrocław, Wybrzeże Wyspińskiego 27, 50-370 Wrocław, Poland); Pacyna, J.; Palczynski, R. J. *Environ Pollut* 14(2): 101-107; 1977.

Strontium-90 and cesium-137 content in human teeth collected in southwest Poland was investigated. The strontium-90 content in deciduous teeth (2.4 pCi/g ash) was four times higher than in permanent teeth (0.6 pCi/g ash), and the cesium-137 content in deciduous teeth (0.09 pCi/g ash) was two times higher than in permanent teeth (0.05 pCi/g ash). The high radionuclide content of deciduous teeth results from the consumption of large quantities of milk by children. The strontium-90 and cesium-137 activity in the diet correlated with the activity in teeth and other human organs. The contamination level in permanent teeth was lower than that in bone. Strontium-90 contents in brain, liver, and gonads were lower than those in bone, teeth, and heart but higher than those in the remaining muscles. A literature review indicated that tooth contamination with the two radionuclides is proportional to the levels in the whole environment, particularly in the atmosphere. It is concluded that tooth contamination is a good measure of the strontium-90 and cesium-137 body burden. (23 refs.)

See also:

\*(Rev.): 78-1838, 78-1839, 78-1841, 78-1842, 78-1843, 78-1847.

\*(Chem.): 78-1933, 78-1995, 78-2092, 78-2093, 78-2094, 78-2095, 78-2096, 78-2097, 78-2098, 78-2099, 78-2100, 78-2101, 78-2102, 78-2103, 78-2104, 78-2105, 78-2106, 78-2107, 78-2108, 78-2109, 78-2110, 78-2111, 78-2112, 78-2113, 78-2114, 78-2115, 78-2116, 78-2117, 78-2118, 78-2119, 78-2120, 78-2121, 78-2122, 78-2123, 78-2124, 78-2125, 78-2126, 78-2127, 78-2128, 78-2129, 78-2130, 78-2131, 78-2132, 78-2133, 78-2134, 78-2135, 78-2136, 78-2137, 78-2138, 78-2139, 78-2140, 78-2141, 78-2142, 78-2143, 78-2144, 78-2145, 78-2146, 78-2147, 78-2148, 78-2149, 78-2150, 78-2151, 78-2152, 78-2153, 78-2154, 78-2155, 78-2156, 78-2157, 78-2158, 78-2159, 78-2160, 78-2161, 78-2162, 78-2163, 78-2164, 78-2165, 78-2166, 78-2167, 78-2168, 78-2169, 78-2170, 78-2171, 78-2172, 78-2173, 78-2174, 78-2175, 78-2176, 78-2177, 78-2178, 78-2179, 78-2180, 78-2181, 78-2182, 78-2183, 78-2184, 78-2185, 78-2186, 78-2187, 78-2188, 78-2189, 78-2190, 78-2191, 78-2192, 78-2193, 78-2194, 78-2195, 78-2196, 78-2197, 78-2198, 78-2199, 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\*(Epid.-Biom.): 78-2370, 78-2371, 78-2372.



## VIRAL CARCINOGENESIS

- 2193 **Marker Rescue of Endogenous Cellular Genetic Information Related to the Avian Leukosis Virus Gene Encoding RNA-directed DNA Polymerase.** (Eng) Cooper, G. M. (Sidney Farber Cancer Inst., Boston, MA, 02115). *J Virol* 25(3): 788-796; 1978.

Endogenous cellular genetic information related to the avian leukosis virus genes encoding RNA-directed DNA polymerase was studied by marker rescue assay to detect the biological activity of subgenomic fragments of virus-related DNA's in uninfected avian cells. Recipient cultures of chicken embryo fibroblasts were treated with sonicated DNA fragments and were infected with LA335 (*pol-ts*), a temperature-sensitive mutant of Rous sarcoma virus that encoded a thermostable DNA polymerase. Wild-type progeny virus were obtained by marker rescue with fragments of DNA of uninfected chicken, pheasant, quail, and turkey cells. The DNA's of these uninfected avian cells, therefore, appeared to contain endogenous genetic information related to the avian leukosis virus DNA polymerase gene. The endogenous *pol*-related genetic information could correspond to endogenous avian leukosis virus-related DNA sequences, endogenous genetic information related to the reticuloendotheliosis virus or *Myxolophus* pheasant virus groups, or to genetic information related to cellular DNA polymerases. (42 refs)

- 2194 **Size and Secondary Structure of Avian Myeloblastosis Virus Associated Ribosomal RNA: Comparison with Cellular and Precursor Ribosomal RNA.** (Eng) Korb, J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Heine, U. *Arch Virol* 56(3): 211-225; 1978.

The mol wt and secondary structures of the viral ribosomal RNA (rRNA) of avian myeloblastosis virus, isolated from the plasma of leukemic chickens, were compared with those of cellular rRNA. The mol wts of viral rRNA ( $1.62 \times 10^6$  and  $0.69 \times 10^6$ ) and cellular rRNA ( $1.63 \times 10^6$  and  $0.67 \times 10^6$ ), the latter obtained from avian myeloblasts, were identical and comparable with the mol wt of chicken liver rRNA. Similarly, the secondary structures of viral rRNA were identical to those of cellular rRNA. The possible precursor character of viral rRNA was excluded because the molecules of viral rRNA did not show any similarity to those of precursor rRNA. (27 refs)

- 2195 **Multiple Forms of *sarc* Gene Proteins from Rous Sarcoma Virus RNA.** (Eng) Kamine, J.

(Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Burr, J. G.; Buchanan, J. M. *Proc Natl Acad Sci USA* 75(1): 366-370; 1978.

A previous study of the RNA translation products of Prague B Rous sarcoma virus (RSV) revealed that two proteins (25,000 and 18,000 daltons) were missing from the translation products of a transformation-defective (*td*) virus mutant that lacks the *sarc* gene. In the present study, the RSV viral RNA's were separated on sucrose gradients, and it was determined that the two putative *sarc* gene products are synthesized as doublets from a messenger RNA (mRNA) of approx 18S. Three other classes of viral mRNA were also found in both the transforming and *td* viruses: (1) a 38S RNA that yields the 80,000-dalton group-specific (*gs*) antigen precursor and the 27,000- and 19,000-dalton *gs* antigens; (2) a 28S RNA that yields a 55,000-dalton protein; and (3) a <8S RNA that yields a 37,000-dalton product. In addition to the 25,000- and 18,000-dalton doublets, there was a 60,000-dalton protein whose synthesis was directed by 18S RNA from transforming RSV. Peptide mapping showed that the 60,000-dalton protein and the 25,000-dalton doublet are structurally related. By means of two-dimensional gel electrophoresis, both bands of the 25,000-dalton doublet were resolved into several species with different isoelectric points. (23 refs)

- 78-2196 **Antiviral Action of a Rifamycin Derivative: Formation of Rous Sarcoma Virus Particles Deficient in 60 to 70S RNA.** (Eng) Szabo, C. (Lab. Chemical Biodynamics, Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720); Bissell, M. J. *J Virol* 25(3): 944-947; 1978.

The antiviral properties of rifazone-8<sub>2</sub> (R-8<sub>2</sub>), a rifamycin derivative, were investigated. Growth of Rous sarcoma virus (RSV)-transformed cells in the presence of R-8<sub>2</sub> resulted in the synthesis of noninfectious virions with an altered buoyant density. Addition of 5 µg/ml R-8<sub>2</sub> to Prague-CRSV-transformed cells resulted in a slight decrease in the synthesis of physical particles and a 60% reduction in focus-forming activity by 2 days after treatment. Addition of 15 µg/ml reduced the infectivity of the virus by >99% after only 1 day, but particle production was decreased more slowly. Thus, R-8<sub>2</sub> affects virus infectivity much more than virus production. Treatment of cells with another derivative, rifampin, had no effect on their reproduction or infectivity, suggesting that the antiviral activity of R-8<sub>2</sub> is due to the lipophilic side chain. Studies with labeled R-8<sub>2</sub> indicated that the drug remained bound to the virus even after extensive purification.



Analysis of the RNA extracted from the noninfectious virus indicated that most of the RNA (>95%) appeared as small species, and only a minor fraction of 60S-70S RNA was detected. The lack of 60S-70S RNA appears to be the ultimate cause of the loss of infectivity. (17 refs)

- 78-2197 Synthesis of Rous Sarcoma Virus-Specific RNA in Chick Embryo Cells.** (Rus) Tatosyan, A. G. (Inst. Experimental Biology, Erevan, USSR); Yakovleva, L. S.; Semenova, L. A.; Kiselev, F. L. *Vopr Virusol* (4): 460-464; 1977.

The synthesis of Rous sarcoma virus (RSV)-specific RNA was studied in commercial chick embryos, leukemia-free chick embryos, and chick fibroblast cultures obtained from leukemia-free embryos and infected with Marek's disease virus (MDV). Isolated RNA specimens were subjected to molecular hybridization with <sup>3</sup>H-DNA-transcripts of RSV synthesized in vitro in the presence of actinomycin D. The <sup>3</sup>H-DNA-transcripts showed 45%-50% hybridization with RNA tumors of chicks infected with RSV, approx 15% hybridization with RNA from commercial embryos, but not hybridization with RNA isolated from chick embryos infected with MDV. (20 refs.)

- 78-2198 Glycoproteins of Avian Tumor Virus Recombinants: Evidence for Intragenic Crossing-Over.** (Eng) Galehouse, D. M. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Duesberg, P. H. *J Virol* 25(1): 86-96; 1978.

The envelope glycoproteins of avian tumor virus recombinants selected for the host range of a leukosis virus and the transforming function of a sarcoma virus were compared with each other and with those of the parental viruses. The recombinants were derived from (1) the Prague subgroup B strain of Rous sarcoma virus (RSV) and a subgroup A leukosis virus (RAV-3) and (2) subgroup A Prague virus and a subgroup B leukosis virus (RAV-2). The glycoproteins of different recombinant viruses derived from the same parents differed in their electrophoretic mobilities measured in polyacrylamide gels. The glycoproteins with lower electrophoretic mobilities had higher percentages of carbohydrate. Based on their buoyant densities in CsCl, the viral glycoproteins contained 8%-18% carbohydrate. After exhaustive Pronase digestion, the carbohydrate was recovered from the glycoproteins as a mixture of glycopeptides with mol wts of 2,500-5,000. Distinct viral glycoproteins contained between two and five oligosaccharide chains, but glycoproteins of different recombinants expressing the same host range marker differed in the number of oligosaccharide chains and, consequently, in their polypeptide structure. Those with a lower electrophoretic mobility contained more oligosaccharide chains per

molecule than those with higher electrophoretic mobility. It is suggested that not all oligosaccharide chains define viral host range. (32 refs.)

- 78-2199 Virus-specific DNA in the Cytoplasm of Avian Sarcoma Virus-infected Cells Is a Precursor of Covalently Closed Circular Viral DNA in the Nucleus.** (E) Shank, P. R. (Dept. Microbiology, Univ. California, San Francisco, CA 94143); Varmus, H. E. *J Virol* 25(1): 104-117; 1978.

Three principal forms of viral DNA were identified in quail cells derived from a methylcholanthrene-induced fibrosarcoma and infected with B77 avian sarcoma virus: (1) a linear duplex molecule synthesized in the cytoplasm, (2) a covalently closed circular molecule found in the nucleus, and (3) proviral DNA covalently linked to high-mol-wt cell DNA. The precursor-product relationships among these viral DNA forms were defined in pulse-chase experiments using bromodeoxyuridine for the density labeling of the linear viral DNA species in the cytoplasm during the first 4 hr after infection. After a 4- to 8-hr chase with thymidine, a portion of the density-labeled viral DNA was transported to the nucleus and converted to a covalently closed circular form. These results demonstrated that the linear viral DNA synthesized in the cytoplasm is the precursor to the closed circular DNA in the nucleus. Whether the latter is the precursor to the integrated provirus remains to be determined. (38 refs.)

- 78-2200 Regulation of Adenosine 3':5'-Monophosphate Content of Rous Sarcoma Virus-transformed Human Astrocytoma Cells. Effects of Cholera Toxin on Responsiveness to Catecholamines and Prostaglandins.** (Eng) Johnson, G. L. (Dept. Medicine, Univ. California, San Francisco, CA, 94143); Harden, T. K.; Lefkowitz, J. P. *J Biol Chem* 253(5): 1465-1471; 1978.

The effect of cholera toxin on the responsiveness of EH18MG cells (from a Rous sarcoma virus-transformed human astrocytoma derived from line 1181N1) to catecholamines and prostaglandins was investigated. The cells usually respond to these substances by an increase in cyclic AMP (cAMP) formation. Cholera toxin treatment (10-100 ng/ml) for 45-60 min resulted in a 5- to 10-fold increase in cellular cAMP content over basal levels. The toxin also decreased the K<sub>0.5</sub> (concentration causing a half-maximal effect) for isoproterenol 10- to 50-fold and decreased that for prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) 30- to 100-fold. However, the maximal response to PGE<sub>1</sub> was increased 1.5- to 3-fold. Treatment with cholera toxin did not change the K<sub>i</sub> values for  $\beta$ -adrenergic receptor antagonists such as propranolol, alprenolol, and sotalol. Direct binding studies with labeled iodohydroxytylpyridinolol indicated no significant changes in the number of  $\beta$ -receptors or in the kinetics of the interaction of the



ligand with receptors after treatment of cells with the toxin. Competition binding studies with propranolol and sotalol revealed no toxin-induced changes in  $K_d$  values for these antagonists. Treatment with the toxin caused only small decreases (2- to 3-fold) in the  $K_d$  values for the binding of alpropratenol and norepinephrine. It is concluded that cholera toxin has little direct effect on the binding of agonists or antagonists to  $\beta$ -receptors, but it does increase the efficiency of coupling of receptor and catalytic moieties of adenylate cyclase. (26 refs)

78-2201 **Molecular Mechanism for the Specific Inhibition of Reverse Transcriptase of Rous Sarcoma Virus by the Copper Complexes of Isonicotinic Acid Hydrazide.** (Eng) Srivastava, A. (Microbiology and Cell Biology Lab., Indian Inst. Science, Bangalore 560012, India); Antony, A.; Ramakrishnan, T. *Biochem Pharmacol* 27(4): 579-584; 1978.

Inhibition of the endogenous and exogenous reverse transcriptase activity of Rous sarcoma virus (RSV) by the copper complexes of isonicotinic acid hydrazide (isoniazid) was examined. As low a final concentration as 50  $\mu$ M of the cupric and cuprous complexes inhibited the endogenous reaction 73% and 75%, respectively. Inhibition of the exogenous reaction varied with the templates. The inhibition could be reversed by either  $\beta$ -mercaptoethanol or EDTA. The specificity of the inhibition was ascertained by using a synthetic primer-template,  $-(dG)_{15}-(rCm)_n$ , which is highly specific for reverse transcriptases. Using different polyribonucleotide and polydeoxyribonucleotide strands as primer-templates, it was demonstrated that both complexes inhibit both steps of reverse transcription. Inhibition of the second step, catalyzed by a polydeoxyribonucleotide primer-template, was greater than that of the first step, catalyzed by a polyribonucleotide primer-template. (14 refs)

78-2202 **Induction of Some Transformation-related Properties by a Transformation-defective Mutant of Avian Sarcoma Virus.** (Eng) Yoshida, M. (Lab. Viral Oncology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo, 170, Japan); Ikawa, Y. *Virology* 83(2): 444-448; 1977.

A transformation-defective (*td*) mutant (TY 9) was isolated from Prague strain Rous sarcoma virus, subgroup C (PR-RSV-C), by UV irradiation and then used to infect chick embryo fibroblasts (CEF). TY 9 induced neither morphological alteration of CEF nor focus formation under an agar layer within 7-9 days under standard conditions. TY 9 RNA had shorter monomers of genomic RNA than the class *a* RNA of the parental PR-RSV-C, but TY 9 RNA migrated slightly lower than the class *b* RNA of *td* PR-C. After repeated transfer, TY 9-infected cells became more fusiform, compared with cells transformed by wild-type PR-C. Infected

cells also had increased saturation density, increased glucose uptake, and colony-forming ability in soft agar, and they produced plasminogen activator. (12 refs)

78-2203 **Simulation of Sarcomas in Primates by Rous Sarcoma Virus.** (Rus) Adzhigitov, F. I. (Inst. Experimental Pathology and Therapy, Sukhumi, USSR). *Vestn Akad Med Nauk SSSR* (8): 88-91; 1977.

The tumorigenicity of Rous sarcoma virus (RSV) was tested in various species of lower primates. RSV-induced tumors developed in 91% of *Macaca rhesus* and in 50% of the African green monkeys and baboons. Newborn monkeys were more susceptible to RSV: approx 60% of the newborns developed sarcoma compared to 33% of the adolescent monkeys (up to 1 yr old). Adult monkeys were resistant to RSV. All tested monkeys could be divided into three groups: Group 1 showed progressive tumor growth; Group 2 showed rapid tumor growth within the first 2-3 wk of inoculation followed by complete tumor regression; Group 3 was resistant to RSV. RSV-induced tumors developed at the inoculation site and had the histology of fibrosarcomas or rhabdomyosarcomas. The high frequency of tumor regression was probably due to the presence of serum antibodies against group-specific antigen. (31 refs.)

78-2204 **Reticuloendotheliosis Virus: Experimental Infection of Poultry and Immunofluorescent Identification of Australian Isolates (Letter to Editor).** (Eng) Bagust, T. J. (CSIRO Div. Animal Health, Private Bag No. 1, P.O. Parkville, Victoria, 3052, Australia); Dennett, D. P. *Aust Vet J* 53(1): 506-508; 1977.

Cell culture of a variety of reticuloendotheliosis viruses (REV) found in Queensland, Australia, is described. An indirect fluorescent antibody (IFA) test was developed that detected antibody to REV and identified two other Australian REV isolates. Using the IFA test, the sequential development of antibodies to REV was detected in 1- to 2-day-old and 2-wk-old chickens and 1-day-old Muscovy ducks previously inoculated ip with REV/Q/1/73. Max serum titers usually occurred 6-10 wk after infection and then declined at varying rates to 14 wk, when final tests were performed. A high proportion (88%) of chickens with disease symptoms had serum samples positive for REV antibody; however, 25% of the symptom-free chickens had REV antibodies. Low levels of antibodies were detected in the REV-infected ducks. The IFA test was used to analyze 586 commercial poultry sera collected from 1973 to 1975, prior to the use of avian vaccines known to be contaminated with REV. It was evident from the results that REV occurs as a natural infection of Australian poultry flocks. (3 refs.)



- 78-2205 Transformation of Chick Embryo Fibroblasts by Reticuloendotheliosis Virus. (Eng) Franklin, R. B. (Dept. Microbiology, Univ. Texas at Austin, Austin, TX, 78712); Kang, C. Y.; Wan, K. M.; Bose, H. R. *Virology* 83(2): 313-321; 1977.

The transformation of chick embryo fibroblasts by a reticuloendotheliosis virus (REV) isolated from a transformed cell line from the bone marrow of an REV-infected chicken is reported. Supernatant fluid from the bone marrow cultures was used as the source of the virus. The fibroblasts were infected with 1.0 ml of REV medium at a multiplicity of infection of 2. By 24 hr, the infected cells were distinctly less extended than the uninfected cells and by 48 hr, the infected cultures showed complete morphological conversion. Their ability to grow to an increased cell density, their increased passage capability, growth in soft agar, increased uptake of 2-deoxy-D-glucose, and tumorigenicity (95%) in 40 2-day-old chicks also confirmed that the fibroblasts had been transformed. Cell-free culture fluid from passage 15 of these cells transformed secondary chicken embryo fibroblast cultures, and chickens inoculated ip with 0.1 ml of the cell-free culture fluid died within 9 days from REV-type lesions. (33 refs)

- 78-2206 Characterisation of Mammary Tumour Virus of Strain ICRC Mouse. (Eng) Karande, K. A. (Biology Div., Cancer Res. Inst., Tata Memorial Centre, Bombay 400012, India); Joshi, B. J.; Talageri, V. R.; Dumaswala, R. U.; Ranadive, K. J. *Eur J Cancer* 14(3): 251-261; 1978.

The mouse mammary tumor virus (MuMTV) isolated and purified from the milk of strain ICRC mice, which are susceptible to the spontaneous development of mammary cancer and leukemia, was characterized. The purified virions banded at a density of 1.17 g/ml in 0%-55% linear sucrose gradient and contained mature B-type particles along with a few C-type particles, as observed by electron microscopy. Ten polypeptides, ranging in wt from 12,000 to 100,000 daltons, were resolved by polyacrylamide gel electrophoresis. Three of these proteins, mol wt 49,000 (p49), 34,000 (p34), and 24,000 (p24), were identified as the major structural proteins on the basis of staining reactions. High titers of MuMTV antigens were detected in the milk plasma of strain ICRC mice. Common antigens were detected in disrupted virions of strains ICRC and C3H(Jax) by immunodiffusion. Strain ICRC was initially a high-cancer-incidence strain (av incidence of mammary cancer and leukemia was 83.9% and 38.2%, respectively), but the tumor incidence decreased substantially by the 45th generation (20% and 16%, respectively). The results indicate that the MuMTV of strain ICRC exhibits characteristics comparable to those of the high-cancer-incidence strain, C3H(Jax), in spite of a significant decrease in the mammary tumor incidence. The increase in mammary cancer following force breeding (up to 70%) indicates that it is the potency of the hormonal stimulus that determines the mammary tumor incidence. (47 refs)

- 78-2207 Retroviral "Terminal Deoxynucleotidyl Transferase" Activity Is Reverse Transcription. (Eng) Marcus, S. L. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Sarkar, N. H. *Virology* 84(2): 242-259; 1978.

Detergent-disrupted preparations of murine mammary tumor virus (MuMTV), Mason-Pfizer monkey virus (MP-MV) and Rauscher murine leukemia virus (RLV) were capable of catalyzing poly(dT) synthesis when only the exogenous primer oligo(dT) was supplied. Analysis of this apparent terminal deoxynucleotidyl transferase (TdT)-like DNA polymerase activity revealed that it had characteristics similar to those of reverse transcriptase. Optimal concentrations of divalent cations and the effect of KCl addition were similar to those observed for reverse transcriptase activity. Sensitivity to inhibition by inorganic phosphate for both TdT-like and reverse transcriptase activity were identical and virion-specific. Sedimentation coefficients of TdT-like and reverse transcriptase activity from each virion were identical. The products of TdT-like and reverse transcriptase reactions were equally sensitive to  $S_1$  nuclease treatment. Disruption of viral cores rendered TdT-like activity almost completely sensitive to RNase treatment. Antisera prepared against MP-MV DNA polymerase inhibited both TdT-like and reverse transcriptase activity to an identical degree. These results suggest that the TdT observed in MuMTV, MP-MV, and RLV is actually reverse transcriptase activity directed by endogenous virion poly(A) annealed to the exogenously provided oligo(dT) primer. (29 refs)

- 78-2208 Production of Unintegrated Mouse Mammary Tumor Virus DNA in Infected Rat Hepatoma Cells Is a Secondary Action of Dexamethasone. (Eng) Riggs, G. M. (Dept. Biochemistry, Univ. California, San Francisco, CA, 94143); Shank, P. R.; Yamamoto, K. R. *J Virol* 26(1): 93-101; 1978.

Dexamethasone ( $10^{-6}$  M) increased the rate of mouse mammary tumor virus (MTV) RNA synthesis in rat hepatoma tissue culture (HTC) cells. This hormonal effect occurred rapidly and appeared to be mediated directly by the glucocorticoid-specific receptor protein. In addition to the viral RNA, unintegrated MTV DNA was also detected in these cells. Unintegrated viral DNA accumulated only in the presence of dexamethasone and was produced with a time course that closely paralleled the increased accumulation of viral RNA. Density labeling of the viral DNA indicated that both strands were newly synthesized, implying a nonsemiconservative mode of replication. Inhibitors of viral RNA synthesis prevented the appearance of unintegrated viral DNA. The findings indicate that the unintegrated viral DNA is synthesized by reverse transcription of MTV RNA and that the production of unintegrated viral DNA after dexamethasone treatment occurs as a secondary consequence of the hormonal effect.



induction of viral DNA synthesis. No unintegrated MTV RNA was detected in mouse mammary tumor cells or mouse lymphoma cells, despite the presence of high levels of viral RNA. (36 refs)

**78-2209 In Vitro Mouse Mammary Tumor Virus Transcription from Chromatin: A System to Study the Mechanism of Action of Glucocorticoid Hormones.** (Eng) Crepin, M. (Institut Pasteur, Departement de Biologie moleculaire, 28, Rue du Dr Roux, 75724 Paris Cedex 15, France). *FEBS Lett* 84(2): 266-270; 1977.

cell-free transcription system consisting of chromatin from mammary tumors of the GR mouse and purified exogenous karyotic RNA polymerase B or endogenous RNA polymerase was used to investigate the in vitro synthesis of mouse mammary tumor virus (MMTV) RNA. More MMTV RNA is transcribed from chromatin with RNA polymerase B than with the endogenous RNA polymerase. This result may be explained by a limiting amount of endogenous polymerase molecules in relation to the 70 MMTV genomes integrated in GR mammary cells. Exogenous calf thymus RNA polymerase B may partially saturate the chromatin template and therefore transcribe the MMTV genomes more efficiently. MMTV RNA synthesis was stimulated by a factor of 10 when chromatin from dexamethasone-treated cells was used. This increase of MMTV RNA synthesis supports the proposal that glucocorticoids stimulate MMTV RNA synthesis directly at the transcriptional level. (19 refs.)

**78-2210 Quantitative Determination of Mammary Tumor Virus in Individual Samples of Mouse Milk.** (Eng) Bistocchi, M. (Istituto di Anatomia e Istologia Patologica, Scuola Medica, Via Roma 57, 56100 Pisa, Italy); Bevilacqua, G.; Nuti, M. *Tumori* 63(6): 525-534; 1977.

The presence of mammary tumor virus (MTV) in milk samples from BALB/cfC3H and BALB/cfRHH mice was quantitated by a method based on light scattering measurements of partially purified MTV preparations, the use of milk from genetically identical virus-free mice as a blank, and the use of a whole-milk fraction to determine the total protein content. The milk was removed by a suction device on days 5-8 after delivery. MTV peaked in the characteristic density region of 1.15-1.20 g/ml in both the 260-nanometer optical density profiles and the protein content profiles. In the latter, however, the MTV peak was partially masked because of an increase in protein content from the heavier to the lighter gradient regions. Variation of the amount of milk removed from 0.25 to 1.25 ml did not modify the results. Thus, this method is suitable for milk specimens with either high or low MTV concentrations. Since the virus particles are always

contaminated by nonviral particles, the use of an identical MTV-free milk sample as a blank allows better quantitation. (9 refs)

**78-2211 Genetic Mapping of Xenotropic Leukemia Virus-inducing Loci in Two Mouse Strains.** (Eng) Kozak, C. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014); Rowe, W. P. *Science* 199(4336): 1448-1449; 1978.

The linkage of genes governing the iododeoxyuridine inducibility of murine leukemia virus in C57BL/10J, B10.BR/SgLi, and BALB/cN mice was studied. Crosses of these mice with noninducible strains indicated that virus inducibility was regularly expressed in F<sub>1</sub> hybrids and that the segregation ratios in the backcross generation were comparable with single gene control. In all cases, virus inducibility was linked to the *Dip-1* locus on chromosome 1 (linkage group XIII). The linkage estimates obtained with C57BL/10 and B10.BR hybrids were not significantly different, but the difference in recombination frequency between BALB/c and C57BL/10 crosses suggested that the virus-inducing loci in these strains may not be at allelic sites, even though they are both on chromosome 1. (16 refs)

**78-2212 Genetic Recombination Between Mouse Type C RNA Viruses: A Mechanism for Endogenous Viral Gene Amplification in Mammalian Cells.** (Eng) Barbauld, M. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014); Robbins, K. C.; Hino, S.; Aaronson, S. A. *Proc Natl Acad Sci USA* 75(2): 923-927; 1978.

Typing immunoassays for *gag* (p15, p12, and p30 proteins), *pol* (reverse transcriptase), and *env* (gp70 glycoproteins) gene products of prototype endogenous viruses (inducible ecotropic BALB:virus-1, inducible xenotropic BALB:virus-2, and noninducible xenotropic NIH-murine leukemia virus) were developed and applied to the analysis of potential C-type virus recombinants. Using this approach, recombinants involving exogenous and endogenous mouse C type viruses were identified and genetically mapped. Analogous techniques were used to investigate the genetic relationships between different classes of endogenous virus that exist within the same mouse cells. Proteins of the inducible class of xenotropic virus exhibited extensive antigenic homology with the *gag* but not the *env* gene products of the ecotropic virus class. The *env* gene-coded glycoproteins of the inducible and noninducible xenotropic virus classes possessed striking antigenic relatedness. These findings indicate that the immunologic relatedness between different endogenous mouse C-type viruses can be localized to specific genes, and they support the concept that the inducible xenotropic virus arose by a mechanism involving genetic recombination. (47 refs)



- 78-2213 RNA Tumor Virus Phosphoproteins: Primary Structural Analysis and Identification of Phosphopeptides.** (Eng) Pal, B. K. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033); Bryant, M. L.; Roy-Burman, P. *J Virol* 25(3): 928-932; 1978.

Two-dimensional tryptic peptide mapping was used to compare the peptide sequences of the pp12 phosphoprotein of cloned ecotropic and amphotropic wild mouse leukemia viruses, strains 1504 and 292. The maps of the two ecotropic isolates were similar to one another, as were the maps of two amphotropic isolates. There was also extensive similarity between the maps of this protein from ecotropic and amphotropic viruses, although characteristic peptide differences were readily recognized. These differences were consistent with the general type specificity of oncovirus phosphoproteins. The pp12 of the field isolate of 292 virus contained five phosphopeptides, and the nonphosphorylated and variously phosphorylated species of this pp12 showed identical peptide maps, indicating differential phosphorylation of a single polypeptide. (20 refs)

- 78-2214 Alteration of Murine Leukemia Virus (MuLV) Cell Surface Antigens by Infection with Exogenous Virus (Meeting Abstract).** (Eng) Wise, K. S. (Univ. Alabama in Birmingham, Birmingham, AL, 35294); Acton, R. T. *Proc Am Assoc Cancer Res* 19: 137; 1978. (no refs)

- 78-2215 The Presence of Disulfide-linked gp70-p15(E) Complexes in AKR Murine Leukemia Virus.** (Eng) Pinter, A. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021); Fleissner, E. *Virology* 83(2): 417-422; 1977.

Electrophoresis of  $^{14}\text{C}$ - and  $^3\text{H}$ -labeled AKR virions under nonreducing conditions indicated the presence of a glycoprotein with a mol wt of 90,000 (gp90). Characterization of gp90 indicated that it is composed of gp70 linked to p15(E) by one or more labile disulfide bonds. It is suggested that gp90 represents the basic unit of the surface structure of the virus. (24 refs)

- 78-2216 Friend Virus-induced Inhibition of Eosinophil Granulocyte Exudation in Mice.** (Eng) McGarry, M. P. (Dept. Biological Resources, New York State Dept. Health, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Styles, B. D.; Mirand, E. A. *J Natl Cancer Inst* 60(4): 803-810; 1978.

The exudation of eosinophil polymorphonuclear WBC (E-

PMN) in response to 0.2 ml of tetanus toxoid (TT) was studied in male DBA/2HaD mice with Friend virus (FV)-induced erythroleukemia. The inhibition of exudation was independent of increased levels of serum corticosteroids, it occurred in surgically adrenalectomized mice. Thus, the inhibition was independent of the steroid-induced effects of E-PMN accumulation of neutrophil PMN (N-PMN) in TT-induced exudates was unaltered. Furthermore, N-PMN exudation response to other inflammatory stimuli was similarly unpaired in virus-infected mice; this confirmed the specificity of the inhibition for E-PMN. The virus entity in the FV complex responsible for the effect was not identified. Friend murine leukemia virus, the indigenous helper virus for the defective spleen focus-forming virus, was not capable of inducing the inhibition by itself. It is suggested that the lack of participation of E-PMN in TT-induced immune inflammatory exudates in FV-infected mice reflects an unresponsiveness that contributes to the development and progression of leukemia in FV-infected mice. (45 refs)

- 78-2217 Nonrandom Inclusion of H-2K and H-2D Antigens in Friend Virus Particles from Mice of Various Strains.** (Eng) Bubbers, J. E. (Dept. Immunology, Scripps Clinic and Research Foundation, La Jolla, CA, 92037); Chen, S.; Lilly, F. *J Exp Med* 147(2): 340-347; 1978.

Friend murine leukemia virus (FLV) isolated from the infectious sera of several H-2-congenic mouse strains was tested for H-2 antigen content by determining its ability to inhibit the lytic activity of anti-H-2K and anti-H-2D antisera. Of six H-2K or H-2D alleles examined, only H-2Db and H-2Dk were detected, and their expression was confined to virus preparations that had been disrupted with Nonidet P-40 detergent. Control preparations from normal mouse serum and virus preparations that had not been disrupted had no H-2 activity. Furthermore, attempts to neutralize FLV spleen focus-forming activity with anti-H-2Db or anti-H-2Kk antisera yielded negative results. (23 refs)

- 78-2218 Relationship Between Organotropism and Leukemogenicity of Type C RNA Virus Demonstrated in NIH Swiss Mice Inoculated at Birth with Gross Murine Leukemia Virus.** (Eng) Nagao, K. (Dept. Pathology, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima 734, Japan); Kodama, Hamada, K.; Yokoro, K. *J Natl Cancer Inst* 60(4): 855-859; 1978.

The relationship of the organ distribution pattern of ecotropic murine leukemia virus and leukemogenesis was examined by XC plaque assay in NIH Swiss mice infected at birth with Gross murine leukemia virus (G-MuLV). The data were compared with literature data obtained for W/Fu rats in



at birth with G-MuLV adapted for rats (G-MuLV-AR). G-MuLV-infected mice developed T-cell leukemia with short latency period. The virus infectivity was detected not only in lymphoid tissues, but also in the muscle, testis, and uterus, in which no overt leukemia cell infiltration was noted. Infectivity was first detected in the thymus and other tissues as early as 7 days after infection, and the titers then increased in many tissues until manifestation of leukemia. No virus was detected in any tissues in noninfected controls up to 18 months of age. In rats infected with G-MuLV-AR, the site of virus replication and of leukemogenesis was confined to the thymus. Cell-free extracts (CFE) from the thymus and spleen of G-MuLV-infected mice injected into newborn syngeneic mice showed prominent leukemogenicity. CFE from the muscle, testis, and uterus, however, were much less leukemogenic or lacked leukemogenicity. Thus, G-MuLV contained leukemogenic and nonleukemogenic viruses as two subpopulations. Lymphoid organs, especially the thymus, appear to be the favored site of the former, and nonlymphoid tissues appear to be the favored site of the latter. (26 refs)

78-2219 **Structure of 50 to 70S RNA from Moloney Sarcoma Viruses.** (Eng) Maisel, J. (Dept. Pediatrics, Univ. California, San Francisco, CA, 94143); Bender, R. C.; Hu, S.; Duesberg, P. H.; Davidson, N. *J Virol* 25(1): 394-394; 1978.

The 50S-70S RNA's of Moloney sarcoma-leukemia virus (MSV) clone 3 from normal rat kidney (NRK) cells and MSV clone 124 from NRK cells were examined for heterodimers. RNA's from both clones contained large monomer subunits approx 10,000 nucleotides long [10 kilobases (kb)] that were thought to be MSV subunits. Both RNA's also contained a smaller, sarcoma-specific subunit either 3 kb (clone 3) or 6 kb (clone 124) long. Electron microscopy of intact 50S-70S dimer molecules from both clones revealed many dimers of two small subunits, some dimers of two large subunits, but no heterodimers with one large and one small subunit. Since the sequences near the 5' end of the RNA subunits are probably homologous between the large and small subunits, a dimer linkage was expected to form. Some small-small dimers migrated anomalously slowly on nondenaturing gels. The nature of this complex is not known; it could be a higher aggregate of the small-small dimer with additional small or large subunits, or it could be an extended conformation of the small-small dimer. It is suggested that the lack of dimer formation is due to lack of homology in regions other than the 5' ends. (10 refs.)

78-2220 **Moloney Leukemia Virus-induced Cell Surface Antigen: Detection and Characterization in**

**Sodium Dodecyl Sulfate Gels.** (Eng) Troy, F. A. (Dept. Biological Chemistry, Univ. California Sch. Medicine, Davis, CA 95616); Fenyo, E. M.; Klein, G. *Proc Natl Acad Sci USA* 74(12): 5270-5274; 1977.

Tumor-associated, virion, and histocompatibility antigens were detected and characterized by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of Triton X-100-solubilized cell-surface components. When coupled to the lactoperoxidase-catalyzed iodination of intact cells, the procedure permits the determination of externally exposed antigens. The method was applied to the Moloney leukemia virus (MoLV)-induced YAC lymphoma cells of strain A mice, which express a MoLV-determined cell-surface antigen (MCSA) in addition to the C-type viral proteins gp71, p30, p15, p15(E), p12, and p10. MCSA was identified as an exposed surface protein distinct in size and antigenic determinants from the major envelope and core proteins of MoLV and the histocompatibility antigens. Multiple mol wt species possessing antigenic determinants for MCSA, gp71, and the histocompatibility antigen H-2a were detected. MCSA activity was associated with proteins possessing three distinct mol wts: 52,000, 92,000 and 180,000-192,000. It is concluded that none of the MCSA activities is associated with either the known MoLV envelope or core proteins or with H-2a. (18 refs.)

78-2221 **Mapping Host Range-specific Oligonucleotides Within Genomes of the Ecotropic and Mink Cell Focus-Inducing Strains of Moloney Murine Leukemia Virus.** (Eng) Shih, T. Y. (Lab. Tumor Virus Genetics, NCI, NIH, Bethesda, MD, 20014); Weeks, M. O.; Troxler, D. H.; Coffin, J. M.; Scolnick, E. M. *J Virol* 26(1): 71-83; 1978.

The recombination site of a mink cell focus-inducing virus strain (Mo-MuLV<sub>83</sub>) derived from an ecotropic Moloney murine leukemia virus (Mo-MuLV) was mapped. Large RNase T1-resistant oligonucleotides were fingerprinted by two-dimensional gel electrophoresis. Mo-MuLV<sub>83</sub>, in contrast to the ecotropic Mo-MuLV, demonstrated a broadened host range (growth on mouse and mink cells), and recombination involved the *env* gene function. The genomic RNA of these two viruses shared 42 out of 51-53 large T1 oligonucleotides (81%) and possessed a similar subunit size of 36S. Most of these T1 oligonucleotides were mapped in their relative order to the 3' polyadenylic acid end of the viral RNA molecules. There were 10 common oligonucleotides immediately next to the 3' termini. Clusters of 7 (in Mo-MuLV<sub>83</sub>) or 10 (in Mo-MuLV) unique T1 oligonucleotides were mapped next to the common sequences at the 3' end, and they all appeared concomitantly in a polyadenylic acid-containing RNA fraction with a sedimentation coefficient slightly larger than 18S. Therefore, the *env* gene of Mo-MuLV was situated approx 2,000-4,000 nucleotides from the 3' end of the genomic RNA, and the gene order of Mo-MuLV appeared to be similar to that of the more rigorously determined avian oncornaviruses.



Complementary DNA specific for the xenotropic sequences in the spleen focus-forming virus RNA hybridized to the cluster of unique oligonucleotides of Mo-MuLV<sub>83</sub> RNA. This suggests that the loci of recombination involve the homologous *env* gene region of a xenotropic virus. (24 refs)

**78-2222 Polypeptide Maps of Cells Infected with Murine Type C Leukemia or Sarcoma Oncovirus.**

(Eng) Strand, M. (Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205); August, J. T. *Cell* 13(2): 399-408; 1978.

The polypeptide composition of murine fibroblast cells and the effect of infection by RNA sarcoma and leukemia viruses were analyzed by two-dimensional gel electrophoresis and tryptic peptide mapping. The polypeptide maps of NIH Swiss mouse embryo fibroblasts (NIH/3T3) and BALB/c mouse embryo fibroblasts (BALB/3T3) were similar except for two major polypeptides of approx 65,000 and 75,000 daltons that were not detected in BALB/3T3 cells. NIH/3T3 cells infected with Rauscher or Gross oncoviruses and outbred Swiss mouse embryo fibroblasts (3T3 FL) contained two major polypeptides of 73,000 and 80,000 daltons not found in uninfected NIH/3T3 cells. Although uninfected, the 3T3 FL cells also contained a high concentration of an endogenous oncovirus envelope glycoprotein. 3T3 FL cells transformed by Moloney sarcoma virus showed changes in many polypeptides, including several major components: the disappearance or modification of a 60,000-dalton component, an increased concentration and shift in the isoelectric point of a 48,000-dalton glycoprotein, and the apparent loss of several smaller polypeptides. The major changes of the transformed cells were not associated with cell-surface proteins labeled by lactoperoxidase-catalyzed iodination. (27 refs)

**78-2223 Multiple RNase H Activities in Mammalian Type C Retrovirus Lysates.** (Eng) Gerard, G.

F. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO, 63110). *J Virol* 26(1): 16-28; 1978.

Three forms of RNase H were isolated from lysates of Moloney murine sarcoma-leukemia virus [M-MSV(MLV)] by polycytidylic acid [poly(C)]-agarose chromatography. RNase H I was associated with RNA-directed DNA polymerase activity and it eluted at 0.23 M KCl. RNase H II eluted at 0.12 M KCl and was not associated with DNA polymerase activity. RNase H II was a random exohydrolase that required free-chain termini in its hybrid substrate for activity. Lysates of Rickard feline leukemia virus also contained RNase H activity that was not associated with DNA polymerase activity and that eluted from poly(C)-agarose at 0.12 M KCl. A third species from M-MSV(MLV) lysates, RNase H III, did not bind to poly(C)-agarose in 0.06 M KCl. This form was purified from lysates of M-MSV(MLV) and M-MLV by sequen-

tial chromatography on poly(C)-agarose, diethylaminoethyl cellulose, phosphocellulose, and polyuridylic acid-Sepharose. The purified enzyme (1) was free of any associated DNA polymerase activity, (2) had an apparent mol wt of 30,000, (3) had an absolute requirement for  $Mn^{2+}$  (1 mM optimum) for the degradation of [<sup>3</sup>H](A)n-(dT)n, (4) was inhibited by the presence of any salt in the reaction mixtures, and (5) was endoribonucleolytic in its mode of action. RNase H III was inhibited by antisera prepared against Rauscher MLV and simian sarcoma virus reverse transcriptase, and the quantities of RNase H II and I present in the lysates of M-MLV were reduced and increased proportionally if the virus was lysed in the presence of phenylmethylsulfonyl fluoride. It is concluded that RNase H III is a proteolytic cleavage product of DNA polymerase-RNase H. Substantial RNase H activity that did not bind to poly(C)-agarose in 0.06 M KCl was found in lysates of Harvey MSV(MLV), Rauscher MLV, Rickard feline leukemia virus, but not in lysates of a myeloblastosis virus. (25 refs)

**78-2224 Binding Characteristics of Rauscher Leukemia Virus Envelope Glycoprotein gp71 to Murine Lymphoid Cells.** (Eng) Fowler, A. K. (NCI, Frederick Cancer Res. Center, Frederick, MD 21701); Twardzik, D.

Reed, C. D.; Weislow, O. S.; Hellman, A. *J Virol* 24(3): 735; 1977.

The major envelope glycoprotein (gp71) purified from Rauscher leukemia virus (R-MuLV) was tested for its ability to bind to murine lymphoid cells (thymus and spleen), murine nonlymphoid cells (RBC and sperm), and lymphoid cells from other species (rat, rabbit, baboon, and man). The glycoprotein bound efficiently to murine lymphoid cells but not to murine nonlymphoid cells or lymphoid cells from the other species. The binding of <sup>125</sup>I-labeled R-MuLV gp71 was competitively inhibited by unlabeled glycoprotein and by whole R-MuLV, but not by murine xenotropic viruses, R-MuLV p30, or several unrelated proteins. Polyacrylamide gel electrophoresis profiles of iodinated gp71 after binding to lymphoid cells were similar to prebound profiles. Antibody to R-MuLV gp71 prevented binding, but normal serum had no effect. Adsorption of the glycoprotein to murine lymphoid cells occurred rapidly and was time- and temperature-dependent. The binding assay detected the receptor activity of approx 10<sup>4</sup> cells. Binding was proportional up to 2.5 x 10<sup>5</sup> cells/ml and it plateaued above 10<sup>7</sup> cells. In the presence of excess R-MuLV gp71, BALB/c thymocytes bound approx 24 x 10<sup>4</sup> molecules/cell. (25 refs.)

**78-2225 Resolution and Characterization of Intracellular Plasmic Forms of Reverse Transcriptase from Rauscher Leukemia Virus-producing Cells.** (Eng) Marcus



(Memorial Sloan-Kettering Cancer Center, New York, NY, 10021). *J Virol* 26(1): 1-10; 1978.

The isolation and characterization of two forms of reverse transcriptase from the cytoplasm of Rauscher leukemia virus-producing cells (JLSV-10) are described. The two enzymatic forms were present in the microsomal supernatant fraction of these cells but not in uninfected JLSV-9 cells. Phosphocellulose chromatography indicated that the enzyme eluting at 0.3 M KCl (PC I) was identical to the enzyme isolated directly from purified virions. PC II, eluting at 0.5 M KCl, was not detectable in the purified virions. The PC II enzyme had a mol wt of 109,000 daltons, compared to 70,000 daltons for the PC I enzyme, and the former could not be further dissociated by exposure to high salt or nonionic detergent. Mixing purified virion or PC I DNA polymerase with uninfected cells followed by fractionation did not produce the PC II form; this indicated that the latter is not an artifact of purification. Both enzymes appeared antigenically similar to virion DNA polymerase, demonstrated identical divalent cation requirements for various template primers, and were capable of copying heteropolymeric regions of rabbit globin messenger RNA. However, the PC II form was far more heat labile than the PC I form. Furthermore, although the PC I and virion-derived enzyme copied poly(C)-(dG)<sub>12-18</sub> efficiently at a template-to-primer ratio of 25:1, the PC II enzyme preferred a ratio of 5:1 for optimal poly(dG) synthesis. It is speculated that PC II is an enzymatically active intermediate in the synthesis of PC I. (34 refs)

78-2226 DNA-dependent-DNA-polymerase: Possible Limiting Influence on Cell Reproduction During Viral Leukemogenesis. (Eng) OKunewick, J. P. (Cancer Res. Unit, Clinical Radiation Therapy Res. Center, Allegheny General Hosp., 320 E. North Ave., Pittsburgh, PA, 15212); Braunschweiger, P. G. *Experientia* 34(1): 108-109; 1978.

The primer-dependent-polymerase (PDP) assay technique was used to study changes in DNA-dependent-DNA-polymerase concentrations and in primer-template within the cell nucleus during leukemogenesis. Female SJL/J mice were inoculated with Rauscher leukemia virus and sacrificed 14 days later. Spleen cell nuclei were labeled with (<sup>3</sup>H)thymidine triphosphate and autoradiographed. The overall PDP labeling index was 4.8 times that for normal control spleen cells, indicating that a greater proportion of leukemic cells than normal cells contained the two minimal requisites for PDP assay and DNA synthesis, primer and polymerase. The mean grain count was increased by a factor of 2, suggesting that the concentration either of one or both was also increased on a per cell nucleus basis. Evaluation of the relative levels of nuclear DNA-polymerase- $\alpha$  by enzyme inactivation using hydroxymercuribenzoate indicated that the amount of enzyme present per labeled cell nucleus was equivalent for the leukemic and normal spleen cells. These findings suggest that polymerase production remains under the control of normal

cell mechanisms during leukemogenesis and that the virus may affect cell proliferation by altering the primer-template levels. (16 refs)

78-2227 Stoichiometry and Specificity of Binding of Rauscher Oncovirus 10,000-Dalton (p10) Structural Protein to Nucleic Acids. (Eng) Schulein, M. (Novo Industri A/S, Novo Alle, DK-2800 Bagsvard, Denmark); Burnette, W. N.; August, J. T. *J Virol* 26(1): 54-60; 1978.

The nucleic acid binding properties of the 8,000- to 10,000-dalton (p10) structural protein of Rauscher oncovirus, encoded by the *gag* gene, were characterized. Purification by size fractionation and affinity chromatography revealed a highly basic protein with an isoelectric point of  $> 9.0$ ; its immunological antigenicity was chiefly group-specific. Study of the protein-RNA complex indicated that a max of approx 140 moles of p10 bound to 1 mole of 35S RNA; this corresponded to about 1 molecule of p10/70 nucleotides. The protein-RNA complex banded at a density of about 1.55 g/ml. The number of nucleic acid sites bound and the affinity of p10 binding differed significantly among the other polynucleotides tested. The protein bound to both RNA and DNA, with a preference for single-stranded molecules. Rauscher virus RNA and single-stranded phage fd DNA contained the highest number of binding sites. Binding to fd DNA was saturated with approx 30 moles of p10/mole fd DNA, an av of 1 p10 molecule/180 nucleotides. The apparent binding constant was  $7.3 \times 10^7$  M<sup>-1</sup>. (39 refs)

78-2228 Separation of the Tumor Rejection Antigen (TSTA) from the Major Viral Structural Proteins Associated with the Membrane of an R-MuLV-induced Leukemia. (Eng) Rogers, M. J. (Lab. Cell Biology, NCI, Bethesda, MD, 20014); Law, L. W.; Prat, M.; Oroszlan, S.; Appella, E. *Int J Cancer* 21(2): 246-252; 1978.

The tumor-specific transplantation antigen (TSTA) of a Rauscher murine leukemia virus (R-MuLV)-induced leukemia (RBL-5) was solubilized from the plasma membranes by sodium deoxycholate. Gel filtration chromatography separated the high-mol-wt fractions containing TSTA from the lower-mol-wt fractions containing the structural proteins gp70 and p30. The antigen reacting with syngeneic serum from mice immunized with RBL-5 membranes was also separated from TSTA. Virolysis experiments suggest that the target of the syngeneic serum was the viral envelope protein p15E. Gel filtration chromatography also separated TSTA from the host histocompatibility antigens. Previous data and those generated by this study suggest that the host antitumor immune response, which is directed against viral structural antigens, does not protect against a progressively growing transplantable tumor. TSTA appears to be a distinct antigen, differing from the viral structural antigens. It is not known



whether this antigen is coded for directly by the viral genome or whether it is virally induced from host genes. (34 refs)

- 78-2229 Membrane Properties of the gag Gene-coded p15 Protein of Mouse Type-C RNA Tumor Viruses.** (Eng) Barbacid, M. (Instituto de Bioquímica de Macromoléculas, Madrid, Spain); Aaronson, S. A. *J Biol Chem* 253(5): 1408-1414; 1978.

The structural constituents of the murine C-type RNA viral membrane were investigated. Of the gag gene-coded proteins of Rauscher murine leukemia virus (MuLV), only p15 exhibited hydrophobic properties characteristic of a membrane protein. Biochemical analysis of Rauscher MuLV p15 indicated the absolute requirement of detergents or phospholipids for maintenance of its native state in aqueous soln. Furthermore, this protein specifically interacted with the micellar structures of several nonionic surfactants and small phospholipid vesicles. Rauscher MuLV p15 was located within the virion in a partially exposed position, as determined by its accessibility to lactoperoxidase but not to immunoglobulin molecules. Thus, Rauscher MuLV p15 is a constituent of the C-type viral membrane. p15 proteins isolated from Gross MuLV, BALB:virus-2, and NIH MuLV were also shown to possess hydrophobic properties and antigenic determinants related to those of Rauscher MuLV p15. Furthermore, each could be specifically labeled in the intact virion. The conservation of the biochemical and immunologic properties of the gag gene-coded p15 among various mammalian C-type viruses suggests an important role for this protein in the viral membrane. (44 refs)

- 78-2230 Characterization of a Retrovirus that Cross-React Serologically with Canine and Human Systemic Lupus Erythematosus (SLE).** (Eng) Quimby, F. W. (Hematology Service, New England Medical Center Hosp., Boston, MA, 02111); Gebert, R.; Datta, S.; Andre-Schwartz, J.; Tannenber, W. J.; Lewis, R. M.; Weinstein, I. B.; Schwartz, R. S. *Clin Immunol Immunopathol* 9(2): 194-210; 1978.

The murine C-type RNA virus, SP104, was characterized. The virus was isolated from a plasmacytoma that developed in a 9-mo-old (BALB/c x A/J)F<sub>1</sub> mouse that had been inoculated at birth with a cell free filtrate of canine spleen. Morphologically, the virus was a C-type virus. It was a typical retrovirus with a buoyant density of 1.15-1.17 g/cm<sup>3</sup>, high mol wt RNA and reverse transcriptase. It contained antigens that cross-reacted with the p30, gp71, p12, and p15 of other murine retroviruses. Biologically, SP104 was a murine B-tropic, weakly oncogenic virus; however, it was efficient in eliciting antinuclear antibody production in mice. Nucleic acid hybridization indicated that the RNA of SP104 had only partial identity with other murine leukemia viruses. Al-

though a viral antigen had been shown previously to cross-react with an antigen present on the surfaces of blood lymphocytes of humans and dogs with systemic lupus erythematosus, there was no evidence that the genetic sequences found in this virus were present in the affected humans and dogs. (37 refs.)

- 78-2231 Correlation Between Polyion Effect on C-Type Viruses and Polyion Effect on Some Membrane-related Functions.** (Eng) Hesse, J. (Inst. Medical Microbiology, Univ. Copenhagen, 22 Julian Maries Vej, DK-2100 Copenhagen O, Denmark); Ebbesen, P.; Kristensen, G. *Int J Virology* 9(3): 173-183; 1977.

The influence of different polyions on infectivity was compared with their effect on membrane-related phenomena. Both diethylaminoethyl-dextran (DEAE-d) and polybrene (each, 25 µg/ml) increased cell susceptibility to viral infection by Kirsten murine sarcoma virus (MSV) and Rauscher murine leukemia virus (MuLV). The maximum enhancing effect of DEAE-d on MSV infectivity lasted an average of 4 hr. Infectivity was not significantly influenced by 25 µg/ml dextran sulfate (d-sulfate), polyphloroglucinol phosphate (137 M), polyphlore phosphate, or polydiethylstilbestrol phosphate. The incubation of NRK cells and XC cells with polyions altered the electrophoretic mobilities of the cells in accordance with the charge of the polyions. Incubation of ARK thymocytes with 25 µg/ml DEAE-d, polybrene, d-sulfate, or 50 IU heparin caused a similar reduction in equilibrium potentials. Cells treated with fluorescent DEAE-d showed diffuse staining which 4 hr later had been modified into a granular fluorescence with unstained areas. Hyaluronidase (250 µg/ml) significantly enhanced both MSV and MuLV infectivity; heat-inactivated hyaluronidase, collagenase, and neuraminidase had no effect. Ca<sup>2+</sup> (20 mM) enhanced MSV infectivity, but Mg<sup>2+</sup> (20 mM) and Na<sup>+</sup> (40 mM) had no effect. Syncytium formation was not influenced by 2.5 µg/ml DEAE-d or polybrene; however, 25 µg/ml d-sulfate or 137 M reduced the number of plaques markedly. Identical results were obtained in another study when polyion-treated cells were cocultivated with uninfected fibroblasts. Since the charges of polyions cannot fully explain their effect on viral infectivity, the effect of membrane-related enzymes should be considered. (27 refs)

- 78-2232 Studies of Murine C-Type Virus Replication in Mouse Teratocarcinoma Cell Lines.** (Fre) Iversen, J. (Laboratoire d'Hématologie expérimentale, Institut de Recherches sur les Leucémies, Centre Hayem, Hôpital Saint-Louis, 2, place du Dr. A.-Fournier, 75475 Paris Cedex 10, France); Debons-Guillemain, M. C.; Canivet, E.; Emanoïl-Ravicovitch, R.; Tavittian, A.; Boiron, J.



*Rev Fr Hematol Blood Cells* 18(2): 383-390; 1977.

The interactions of murine C-type viruses with cell lines established from a mouse teratocarcinoma were studied. Two embryonal carcinoma cell lines and two differentiated cell lines were used. The former were not susceptible to infection by Moloney sarcoma virus or the Moloney, Gross, or Friend leukemia viruses. However, differentiated cells were fully permissive for the replication of these viruses. The relationships between cell differentiation and susceptibility to C-type viruses are discussed. (19 refs.)

**78-2233 Leukemogenic Activity of Thymotropic, Ecotropic, and Xenotropic Radiation Leukemia Virus Isolates.** (Eng) Haas, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel). *J Virol* 25(3): 705-709; 1978.

Thymotropic, ecotropic, and xenotropic radiation leukemia viruses were tested for their ability to induce leukemia in susceptible mice. These viruses were isolated from the 17BL/6 mouse radiation leukemia system and propagated in culture. B6 mice received intrathymic injections of  $2 \times 10^5$  infectious units of the virus isolates, and half the animals were immunosuppressed by whole-body x-irradiation at 2 days postinjection. Ecotropic virus replication was detectable for 4 wk, but it was significantly diminished at 90 days, at which time the mice had large thymic leukemias. Thymotropic virus replication affected essentially all thymocytes and was noted at all times postinjection. Xenotropic virus infection elicited limited virus replication. B6 mice were then inoculated with various single virus isolates and virus combinations. The results indicated that only the thymotropic virus was leukemogenic in vivo. The leukemogenic capacity of the thymotropic virus alone was increased by simultaneous inoculation with ecotropic virus, indicating that the latter could serve as a helper for the former. (15 refs)

**78-2234 Metabolism of the Pancreatic Carcinogen N-Nitroso-bis(2-oxopropyl)amine after Oral and Intraperitoneal Administration to Syrian Golden Hamsters: Brief Communication.** (Eng) Gingell, R. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42d St. and Dewey Ave., Omaha, NB, 68105); Pour, P. *J Natl Cancer Inst* 60(4): 911-913; 1978.

The metabolism of N-nitroso-bis(2-oxopropyl)amine (BOP) was studied in Syrian golden hamsters following ip and po administration (100 mg/kg; 20 mg/ml in water). The levels of BOP and its metabolites were compared in the urine, blood, bile, and pancreatic juice. Following po administration, the urinary levels of N-nitroso-(2-hydroxypropyl)-(2-oxopropyl)amine (HPOP) and N-nitroso-bis(2-

hydroxypropyl)amine (BHP) peaked at 2 hr; after ip administration, these levels were considerably higher and they increased over 3 hr. HPOP was the major metabolite in the blood, and blood levels were considerably higher after ip than po administration. No BOP was found in the pancreatic juice following po or ip administration; HPOP was the major metabolite in each case, and levels were considerably higher following ip administration. The levels of HPOP and BHP in the bile were higher following ip than po administration, but unchanged BOP was present in each case. These findings suggest that HPOP is the proximate pancreatic carcinogenic metabolite of BOP. It is suggested that this carcinogen is absorbed directly from the pancreatic juice by the ductal cells. The reason for the high incidence of bile duct tumors following po BOP is unknown. (6 refs)

**78-2235 Tumors in Hydrocortisone-treated Mice Inoculated with Polyoma Virus Transformed Hamster Cells.** (Fre) Raynaud, J. (Laboratoire Pasteur, Embryologie experimentale, 20, rue des Moulins, 95110 Sannois, France); Paulin, D.; Cuvillier, L. *C R Acad Sci [D] (Paris)* 285(14): 1267-1269; 1977.

To study the effect of hydrocortisone (H) on the induction of tumors by polyoma-virus transformed BHK hamster cells (Py BHK), XVII and C3HfXVII mice were given transformed and nontransformed cells and H according to three experimental protocols: (1) sc injection of 0.66 mg H every 2 days, sc inoculation of  $5 \times 10^6$  Py BHK cells at the time of the fourth H injection, and two additional injections; (2) sc  $5 \times 10^6$  PY BHK cells and no H; (3) H in same doses as Group 1 and  $5 \times 10^6$  normal BHK cells; (4) H in same doses as Group 1. No tumors or precancerous conditions were observed in mice in groups 2, 3, or 4 up to 25-30 days postinoculation. Tumors appeared on the 10th day after inoculation in 12/12 XVII mice and 4/6 C3HfXVII mice in Group 1. Immunofluorescent studies of mouse embryo cells cultured with a filtrate prepared from the tumors revealed the presence of polyoma virus. Karyotyping of the tumor cells demonstrated that they were hamster cells and not mouse cells. Whether H activated the viral genome of the transformed or the host cell was not determined. (17 refs.)

**78-2236 Chicken Embryo Lethal Orphan (CELO) Virus DNA Present in Hamster Cell Lines Derived from CELO-induced Hepatomas.** (Eng) May, J. T. (Dept. Microbiology, La Trobe Univ., Bundoora, Victoria 3083, Australia); Welsh, J. K.; Asch, B. B.; McCormick, K. J. *Intervirology* 9(5): 321-324; 1978.

The renaturation kinetics of the isolated DNA fragments of chicken embryo lethal orphan (CELO) virus generated by the restriction enzyme EcoRI was measured in the presence of



DNA extracted from two lines of CELO virus-induced hamster hepatoma cells and from control hamster cells. One hepatoma cell line (CILT-2), which does not produce the CELO virus tumor (T) antigen, lacked sequences from about half the virus genome (the  $10.2 \times 10^6$  and  $5.7 \times 10^6$  mol wt fragments). The other hepatoma cell line (CEHEP), which does produce the CELO virus T antigen, lacked sequences corresponding to one-fifth the viral genome ( $< 1$  copy of the  $10.2 \times 10^6$  mol wt fragment). The  $5.7 \times 10^6$  mol wt EcoRI fragment is located at the end of the CELO virus DNA, as previously established by EcoRI cleavage and separation by polyacrylamide gel electrophoresis and electron microscopy. It is suggested that the gene involved in CELO T-antigen production is located at one end of the virus genome, within the  $5.7 \times 10^6$  mol wt fragment. (10 refs.)

- 78-2237 Analysis of Cytoplasmic RNA and Polyribosomes from Feline Leukemia Virus-infected Cells.** (Eng) Conley, A. J. (Marjorie B. Kovler Viral Oncology Labs., Univ. Chicago, Chicago, IL, 60637); Velicer, L. F. *J Virol* 25(3): 750-763; 1978.

Intracellular RNA specific for the Rickard strain of feline leukemia virus (R-FeLV) and polyribosomes from a chronically infected feline thymus tumor cell line (F-422) were analyzed to quantitate virus-specific RNA within the subcellular fractions of infected cells, identify the size classes of intracytoplasmic virus-specific RNA, and determine the presence of virus-specific and nascent protein in the polyribosomes. Cytoplasmic, polyribosomal, and nuclear RNA's were found to be 2.1%, 2.6%, and 0.7% virus-specific, respectively. The cytoplasmic fraction contained a 28S size class, which corresponds to the size of virion subunit RNA, and 36S, 23S, and 15S-18S RNA species. The virus-specific 36S, 23S, and 15S-18S species, but not the 28S RNA, were present in both the total and polyadenylic acid-containing polyribosomal RNA. Anti-FeLV gamma globulin bound to rapidly sedimenting polyribosomes, with the peak binding at 400S. R-FeLV complementary DNA hybridized to RNA in two polyribosomal regions (approx 400S-450S and 250S) within the polyribosomal gradients before, but not after, EDTA treatment. The 400S-450S polyribosomes contained three major peaks of virus-specific RNA at 36S, 23S, and 15S-18S, but the 250S polyribosomes contained predominantly 36S and 15S-18S RNA. There may also be a minor subunit of approx 36S in virion RNA. (67 refs)

- 78-2238 Experimental Horizontal Transmission of Feline Leukemia Viruses of Subgroups A, B, and C.** (Eng) Sarma, P. S. (Lab. RNA Tumor Viruses, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD, 20014); Log, T.; Skuntz, S.; Krishnan, S.; Burkley, K. *J Natl Cancer Inst* 60(4): 871-874; 1978.

The horizontal transmission of the three envelope antigen types (A, B, and C) of feline leukemia virus (FeLV) was investigated in cats housed in isolation units. Blood smears collected at weekly intervals were examined by the fixed-cell, indirect immunofluorescence test for FeLV internal p30, to follow the spread of infection from inoculated cats to control cats. The results indicated that viruses of all three subgroups were transmitted horizontally among kittens and adults with slightly varying degrees of speed. Virus was reisolated from one horizontally infected contact cat in each group, and the envelope antigenic type was the same as that originally inoculated into one cat of the same group. After the cats acquired the infection, they remained viremic during the 9- to 11-month observation period. One cat failed to acquire viremia with FeLV-B, but at the conclusion of the experiment, he was found to have virus-neutralizing, type-specific envelope antibodies against FeLV-B and feline oncornavirus-associated cell membrane antigen. However, serum obtained prior to the experiment revealed no envelope antibodies. This negative finding is thought to be due to a transient viremic infection. (26 refs)

- 78-2239 Bovine and Ovine Leukemia Viruses. I. Characterization of Viral Antigens.** (Eng) Rohde, V. (Institut für Virologie, Fachbereich Humanmedizin, Justus-Liebig-Universität Giessen, 63 Giessen, W. Germany); Pauli, C.; Paulsen, J.; Harms, E.; Bauer, H. *J Virol* 26(1): 159-164; 1978.

The relationship between bovine and ovine leukemia virus was studied by biochemical characterization of the virus-specific proteins. The studies revealed three shared proteins. Two of these, gp60 and gp32, with mol wts of 60,000 and 32,000 daltons, respectively, were glycoproteins but the third, p21 (mol wt 21,000 daltons), was not. Immunological cross reactions suggested that these two leukemia viruses are genetically highly related. (24 refs)

- 78-2240 Isolation of a Precipitating Glycoprotein Antigen from Cell Cultures Persistently Infected with Bovine Leukemia Virus.** (Eng) Phillips, M. (Natl. Animal Disease Center, P. O. Box 70, Agricultural Res. Service, U.S. Dept. Agriculture, Ames IA 50010); Miller, J. M.; Van Duyn, M. J. *J Natl Cancer Inst* 60(1): 213-217; 1978.

A procedure was developed for the isolation of ether-sensitive bovine leukemia virus (BLV)-associated antigen from fluid from BLV-infected fetal lamb kidney cell cultures, and the antigen was characterized. The antigen was precipitated with ammonium sulfate, chromatographed on concanavalin A sepharose, and eluted with  $\alpha$ -methyl-D-mannoside. Gel filtration indicated that the highest activity was centered in the 60,000 dalton elution region. Subjection of the antigen to sodium dodecyl sulfate-polyacrylamide gel



electrophoresis revealed that the activity was attributed to a 58,000 dalton protein. Its glycoprotein nature was confirmed by carbohydrate-positive staining. The isolated BLV glycoprotein antigen did not contain human or bovine proteins. On the basis of these findings, the glycoprotein antigen was designated gp58; it probably corresponds to the gp60 antigen recently identified in BLV. (18 refs.)

**78-2241 Papova-virus in Human Laryngeal Papillomas.** (Eng) Spoendlin, H. (Universitätsklinik für Hals-, Nasen- und Ohrenkrankheiten Innsbruck, A-6020 Innsbruck, Austria); Kistler, G. *Arch Otorhinolaryngol (NY)* (3/4): 289-292; 1978.

Electronically removed tumor specimens from 12 patients with laryngeal papilloma were examined at the light and electron microscope level in an attempt to demonstrate papovavirus particles. In two cases, tissue transplantation was tried successfully in nude (thymus-dysgenetic) mice. In only 1/12 cases was a papova-type virus clearly demonstrated. The patient was a boy in whom a slowly growing laryngeal papilloma was removed twice, at ages 5 and 10 yr. The round particles had a diameter of 45 nanometers and they were generally scattered throughout the nucleoplasm. Occasionally a crystalline arrangement in nuclear areas with low electron density could be observed exclusively in the light microscope of the upper stratum spinosum. The particles could be found in 2% of the cells in this layer, indicating that the morphological demonstration of papovaviruses in laryngeal papilloma is only rarely possible. These findings, coupled with those of other authors, suggest that papovaviruses can be demonstrated in only 1/10 cases of laryngeal papilloma. However, the repeated and unequivocal demonstration of papovaviruses in some cases of laryngeal papilloma seems to be more than a coincidence and can be accepted as evidence for the viral etiology of this tumor. (no refs)

**78-2242 Fine Structure of Polyoma Virus DNA.** (Eng) Griffin, B. E. (Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England). *J Mol Biol* 117(2): 447-471; 1977.

The fine structure of polyoma DNA was mapped based on cleavage with several restriction endonuclease (including *Hae* III and III, *Bam*I, *Hind*II and III, *Bul*I, *Hpa*II, and *Hph*I) and depurination analyses of polyoma DNA, the eight *Hpa* restriction fragments, and some *Hae* fragments. Analysis of the sequences around the origin of DNA replication of polyoma virus showed certain similarities to sequences reported for the origin of replication of SV40. This fine-structure mapping of polyoma DNA has been useful for probing the variability among polyoma strains and analyzing variants and defective species. The next stage for analysis and

comparison must go beyond sequence patterns to the actual primary sequences. (59 refs.)

**78-2243 Polyoma Virus Defective DNAs. I. Physical Maps of a Related Set of Defective Molecules (D76, D91, D92).** (Eng) Lund, E. (Dept. Physiological Chemistry, Univ. Wisconsin Medical Center, 1215 Linden Dr., 589 Medical Science Building, Madison, WI 53706); Fried, M.; Griffin, B. E. *J Mol Biol* 117(2): 473-495; 1977.

Three related polyoma virus species, D92 (92% the size of full-length polyoma virus DNA), D91 and D76, were analyzed by restriction endonuclease cleavage, depurination fingerprinting, and DNA-DNA hybridization, and their structures were compared with that of polyoma wild-type (A2) virus DNA. D92 appeared to contain continuous viral sequences from 1 to 72 map units on the A2 physical map; ie, the entire late region and part of the early region of the viral DNA. D91 and D76 contained similar continuous sequences, except that at 18.0 map units 1% of the DNA was deleted. All three of the defective molecules appeared to be made up in part of rearranged viral sequences. The defective DNA's also appeared to be composed entirely of viral sequences (no host DNA sequences were detected). The following features of the rearranged sequences in the defective DNA's were noted: (1) sequences from the region around 67 map units were linked to other (noncontiguous) regions of the DNA; (2) sequences from about 72 map units were linked to sequences from about 1 map unit; and (3) multiple copies of sequences from 67 to 72 map units (from around the origin of DNA replication) were found (4 copies in D91 and D92, and 2 copies in D76). The mechanism for the generation of defective molecules is not clear, although the presence of exact tandem duplications of sequences is compatible with a previous hypothesis concerning their generation by deletion from large oligomeric forms of DNA. (32 refs.)

**78-2244 Polyoma Virus Defective DNAs: II. Physical Map of a Molecule with Rearranged and Reiterated Sequences (D74).** (Eng) Lund, E. (Dept. Physiological Chemistry, Univ. Wisconsin Medical Center, 1215 Linden Drive, 589 Medical Science Building, Madison, WI 53706); Griffin, B. E.; Fried, M. *J Mol Biol* 117(2): 497-513; 1977.

The structure of the polyoma virus defective species D74 (74% the size of full-length polyoma virus DNA) was determined by DNA-DNA hybridization, restriction endonuclease cleavage, and analysis of depurination products and compared with that of polyoma virus A2 DNA. D74 appeared to be composed entirely of viral DNA sequences (no host DNA sequences were detected). It was made up of three DNA segments, each about 24%, 24%, and 27% in size. The two 24% segments seemed identical; the 27% segment appeared to contain one copy of all the sequences found in the



24% fragments as well as a duplication of some of the sequences. When compared to the physical map of A2 DNA, each segment was composed of viral sequences from 1 to 19 map units, 67 to 69 map units, and 70 to 72 map units. Three features described for the polyoma virus defective species D76, D91, and D92 were also found in D74: (1) sequences from the region around 67 map units were linked to other noncontiguous viral sequences; (2) sequences at 72 map units were linked to sequences at 1 map unit; and (3) multiple copies of sequences from around the origin of viral DNA replication were present. Studies of other polyoma virus defective molecules have indicated that the origin of DNA replication for polyoma virus lies within the sequences from 67 to 72 map units. Since D74 replicates efficiently in the presence of a helper virus but lacks the sequences between 69 to 72 map units, the origin of DNA replication appears to be within 67 and 69 map units and/or 70 and 72 map units. (11 refs.)

**78-2245 Polyoma Virus-specific RNA Synthesis in an Inducible Line of Polyoma Virus-transformed Rat Cells.** (Eng) Manor, H. (Dept. Biology, Technion-Israel Inst. Technology, Haifa, Israel); Kamen, R. *J Virol* 25(3): 719-729; 1978.

The polyoma virus (Py)-specific RNA present in transformed rat LPT cells was characterized before and after mitomycin C (MMC) induction by hybridization with <sup>32</sup>P-labeled separated E and L strands of Py DNA restriction endonuclease fragments. In clone 1A cells maintained under normal growth conditions, the cytoplasm contained a transcript of the E-strand DNA similar to that identified in lytically infected cells, as well as minor quantities of RNA complementary to < 50% of the L- and E-strand DNA from the late region. Nuclei of normally growing cells contained the same species found in the cytoplasm, as well as an additional abundant RNA complementary to one-half of the L-strand DNA from the late region. No significant changes occurred in the cytoplasmic viral RNA after MMC treatment before the onset of viral DNA replication, but the concentration of the nuclear L-strand DNA transcript diminished. After the onset of viral DNA replication following MMC treatment, transcripts of virtually the entire L-strand DNA were found in the nuclei, and the amount of RNA transcribed from the E strand of the early region increased 10-fold. In the cytoplasm, the amount of the early RNA increased about 25-fold; there was a similar increase in the late RNA complementary to the L-strand DNA of the late region. The synthesis of both the early and the late RNA species was inhibited if viral DNA replication was blocked by 5-fluorodeoxyuridine. Thus, induction of viral DNA replication in LPT cells is not determined at the level of messenger RNA synthesis. (24 refs)

**78-2246 2'-Deoxy-2'-Azidocytidine Inhibits the Initiation of Polyoma DNA Synthesis.** (Eng) Bjursell,

G. (Dept. Human Genetics, Univ. Aarhus, DK-8000 Aarhus C, Denmark); Skoog, L.; Thelander, L.; Soderman, U. *Proc Natl Acad Sci USA* 74(12): 5310-5313; 1977.

The inhibition of DNA synthesis by the nucleoside 2'-deoxy-2'-azidocytidine (Cz) was investigated in polyoma-infected 3T6 cells. Four hours after Cz was added to polyoma-infected cell cultures, DNA synthesis in Cz-treated cultures was 10% that in control cultures. Electron microscopy of viral DNA extracted from the inhibited cultures indicated that inhibition resulted in a 5.5-fold decrease in the amount of replicating intermediates (RI). The results indicate that replication is inhibited at an early step, possibly in the initiation of new rounds of replication. The effect on the elongation of DNA chains appeared to be less pronounced. As a result of the inhibition, polyoma DNA molecules in an early stage of replication accumulate in the nuclei. Upon incubation of these nuclei, DNA synthesis is induced. The replication starts from the normal origin, and elongation proceeds bidirectionally at a rate close to that observed in vivo. Analysis of polyoma DNA replication in nuclei isolated from control cells indicates that both initiation and termination of replication are impaired in vitro. (20 refs.)

**78-2247 Effects of 2'-Deoxy-2'-azidocytidine on Polyoma Virus DNA Replication: Evidence for a Rolling Circle-Type Mechanism.** (Eng) Bjursell, G. (Inst. Human Genetics, Univ. Aarhus, DK-8000 Aarhus C, Denmark). *J Virol* 26(1): 136-142; 1978.

The replication of polyoma virus DNA was studied in infected mouse 3T6 cells. Following inhibition of DNA synthesis with 2 mM 2'-deoxy-2'-azidocytidine (Cz), rolling circle-type molecules were found in the infected cells. The circular DNA molecules were always relaxed and of polyoma length. Most of the attached tails were < 2 times the length of the polyoma genome, but tails with a length of up to 4.75 times the genome were also found. Following cleavage of the total pool of replicating molecules with either endo R-EcoRI or endo BamHI, Y-shaped molecules with replicated portions of various lengths were generated from rolling circle-type molecules. After cleavage, Y-shaped molecules with three unequal arms were found that could be explained as being derived from the tail in rolling circle-type molecules starting from the normal origin (29% from the endo R-EcoRI cleavage). Rolling circle-type molecules were also found during a normal, uninhibited infection cycle. In such cells, a relatively higher frequency of rolling circle-type molecules was observed late during infection. Compared with control cultures inhibited by Cz showed a greater amount of rolling circle-type molecules relative to normal replicative intermediates. Since Cz inhibits the initiation of new rounds of replication, the rolling circle-type mechanism is independent of reinitiation of DNA synthesis. (18 refs)

**78-2248 Effect of 5-Bromo-2'-deoxyuridine on the Initiation of DNA Synthesizing Activity of Polyoma Virus.** (Eng) Bjursell, G. (Inst. Human Genetics, Univ. Aarhus, DK-8000 Aarhus C, Denmark); Skoog, L.; Thelander, L.; Soderman, U. *J Virol* 26(1): 143-148; 1978.



**Virus-infected Cells.** (Eng) Zemla, J. (Inst. Virology, Slovak Acad. Sciences, 809 39 Bratislava, Czechoslovakia); Petrik, J. *Acta Virol (Praha)* 22(1): 11-20; 1978.

The in vitro synthesizing activity of uninfected and polyoma virus-infected mouse embryo (ME) cells was investigated by measuring the incorporation of <sup>3</sup>H-thymidine (TdR) into acid-insoluble material in cell-free extracts. In uninfected cells, TdR incorporation was markedly stimulated by the addition of calf thymus DNA slightly stimulated by 2-mercaptoethanol, and very greatly stimulated (100 times) by dithiothreitol (DTT). Virus infection at a multiplicity of infection of 40 plaque-forming units per cell caused a several-fold increase in the enzyme activity of the cells. If the cultivation medium contained 5-bromo-2'-deoxyuridine (BUdR: 100 µg/ml) instead of TdR (100 µg/ml), the virus stimulatory effect was much greater. The enzyme activity of uninfected control cells was not affected by BUdR or TdR. These results emphasize the importance of de novo synthesized viral and/or cellular DNA in regulating the induction of enzymes participating in DNA synthesis. (28 refs)

**78-2249 Formation of Okazaki Fragments in Polyoma DNA Synthesis Caused by Misincorporation of Uracil.** (Eng) Brynolf, K. (Biochemistry Dept. I, Medical Nobel Inst., Karolinska Inst., S-10401 Stockholm, Sweden); Eliasson, R.; Reichard, P. *Cell* 13(3): 573-580; 1978.

The effects of uracil incorporation on polyoma virus DNA synthesis in infected nuclei were investigated. Replacement of deoxythymidine triphosphate (dTTP) by deoxyuridine triphosphate (dUTP) during viral replication in isolated nuclei resulted in radioactivity from labeled deoxynucleoside triphosphates being recovered almost exclusively in very short Okazaki fragments. Incorporation also ceased after a short period of time. Addition of uracil, an inhibitor of uracil-DNA glycosylase, increased total synthesis and shifted the incorporation to longer progeny strands. The presence of as little as 0.5% of dUTP in a dTTP-containing system gave a distinct increase in isotope incorporation into Okazaki pieces accompanied by a corresponding decrease in longer strands. The effect was completely reversed by uracil, and short strands formed from dUTP could be efficiently chased into long strands. These findings suggest that dUTP can be incorporated in place of dTTP into polyoma DNA and that polyoma-infected nuclei contain an excision-repair system that, by removal of uracil, causes strand breakage and under certain circumstances may contribute to the formation of Okazaki fragments. However, other excision-repair mechanisms, not necessarily involving uracil incorporation, may occur and contribute to the generation of Okazaki fragments. (34 refs)

**78-2250 Nucleotide Sequence of the DNA Replication Origin for Human Papovavirus BKV: Sequence**

**and Structural Homology with SV40.** (Eng) Dhar, R. (Lab. DNA Tumor Viruses, NCI, Bethesda, MD, 20014); Lai, C. J.; Khoury, G. *Cell* 13(2): 345-358; 1978.

DNA and RNA sequencing techniques were used to obtain the sequence surrounding the origin of DNA replication for human papovavirus BKV. The structure was characterized by a true palindrome of 17 residues followed by two sets of symmetrical sequences and a stretch of 20 AT residues. Within the two symmetrical sequences was a segment containing a strong purine bias, 23/26 nucleotides. These structures were similar to those found in the region of the simian virus 40 (SV40) replication origin. Within the homologous DNA segments, 60%-80% of the BKV and SV40 nucleotides were the same. The remarkable similarity of BKV and SV40 sequences containing the origins of DNA replication confirms previous suggestions of an evolutionary relationship between the two genomes. In addition, topological similarities between these sequences suggest the possibility of certain structural requirements for bidirectional replication origins in these superhelical DNA's. (60 refs)

**78-2251 Observations on the Growth and Plaque Assay of BK Virus in Cultured Human and Monkey Cells.** (Eng) Seehafer, J. (Dept. Biochemistry, Univ. Alberta, Edmonton, Alberta, Canada T6G 2H7); Carpenter, P.; Downer, D. N.; Colter, J. S. *J Gen Virol* 38(2): 383-387; 1978.

An attempt was made to develop a reliable plaque assay for BK virus (BKV) on cultured human embryo kidney (HEK), muscle (HEM), and lung (HEL) and monkey BSC-I and VERO cells. Monolayer cultures were infected at an input multiplicity of 128 hemagglutinating units/cm<sup>2</sup> of monolayer and harvested at 7-day intervals. HEK, HEM, and HEL cells were capable of supporting BKV replication through passage levels 9, 7, and 6, respectively. Separate experiments indicated that HEM and HEL cells could support virus replication through 12 passages. The yield of virus in VERO cells was approx the same as that in HEK, HEM, and HEL cells, but it was somewhat higher at a higher input multiplicity. BSC-I cells had the lowest yields, even at higher multiplicities. All cell types were then tested in plaque assays for BKV. With HEK, plaques were formed in the third, fourth, and fifth passage levels; optimal time for staining HEK cell monolayers was 19-20 days postinfection. Plaques were never observed in HEM or HEL cells. With BSC-I cells, BKV plaque counts were obtained 27-35 days postinfection. BKV also produced plaques in VERO cells by 20 days, but they were poorly defined. Although HEK and BSC-I cells produced the same virus titers, HEK cells were preferable because the plaques could be counted by 20 days. (12 refs)

**78-2252 T Antigen of BK Papovavirus in Infected and Transformed Cells.** (Eng) Farrell, M. P. (Dept.



Bacteriology and Immunology, Central Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514); Mantyjarvi, R. A.; Pagano, J. S. *J Virol* 25(3): 871-877; 1978.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used to analyze proteins immunoprecipitated from permissive cells infected with BK virus (BKV) and from several cell lines transformed by BKV. Either BKV or simian virus 40 T antisera could precipitate a polypeptide with a mol wt of 86,000 daltons from BKV-infected monkey kidney (Vero) cells and BKV-transformed hamster cells. Using a line of BKV-transformed rat cells, however, polypeptides with mol wts of 86,000 and 92,000 daltons were identified. These polypeptides could be labeled with  $^{35}\text{S}$ -methionine or  $^{32}\text{P}$ . In some experiments, an additional protein of mol wt 55,000 daltons was observed in both transformed and nontransformed rat and hamster cells using both T antisera. However, it did not always appear when double-antibody immunoprecipitation was used. (24 refs)

**78-2253 Preparation of Large Quantities of Separated Strands from Simian Virus 40 DNA Restriction Fragments by Low-Temperature Low-Salt Agarose Gel Electrophoresis.** (Eng) Perlman, D. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Huberman, J. A. *Anal Biochem* 83(2): 666-677; 1977.

A method for the preparation of large quantities of separated strands from simian virus 40 DNA restriction fragments produced by *Hind*II and III or by *Eco*RI and *Hpa*II digestion is described. Existing procedures were modified slightly to eliminate the problematic renaturation of DNA during electrophoresis. Changes in both salt concentration and temperature affect strand separation. A combination of low temperature and low buffer concentration during electrophoresis improved the resolution of the DNA strands. This procedure has allowed the recovery of as much as 200  $\mu\text{g}$  DNA in a single preparative experiment. Use of this technique to study simian virus 40 DNA replication indicated that a semidiscontinuous mechanism is involved. (8 refs)

**78-2254 Nucleotide Sequences of DNA Encoding the 3' Ends of SV40 mRNA. I. The Sequence of the DNA Fragment *Hind*II,III-G.** (Eng) Zain, B. S. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Thimmapaya, B.; Dhar, R.; Weissman, S. M. *J Biol Chem* 253(5): 1606-1612; 1978.

The DNA sequences encoding the 3' ends of simian virus 40 (SV40) messenger RNA (mRNA) were studied using restriction endonuclease fragments. With this technique, the nucleotide sequence of approx 13% of SV40, extending from the DNA coding for the translated portion of early mRNA through that coding for the 3' end of the translated portion

of late mRNA, was confirmed. This sequence, which corresponds to the DNA fragment *Hind*II,III-G, is presented. (refs)

**78-2255 On the Nucleoprotein Core of Simian Virus 40.** (Eng) Martin, R. G. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD, 20014). *Virology* 83(2): 433-437; 1978.

A model of the nucleoprotein core of simian virus 40 (SV40) is presented. The model is consistent with the known dimensions of nucleosomes, it can account for the packaging of nucleosomes per virion, it allows the packing of a closed double-stranded molecule of DNA, and its diameter (approx 7 A) matches that of the av internal volume of the SV40 capsid. Furthermore, if the upper limit value for the internal volume is correct, it would be possible to separate the histone spheres in the model by approx 7 A, even if they were 70 A in diameter, which would eliminate any requirements for a groove. (24 refs)

**78-2256 Genomic Nucleotide Sequence Divergence among the Provirus of Cells Infected with Simian Sarcoma Virus: An Analysis by Nucleic Acid Hybridization (Meeting Abstract).** (Eng.) Kaufman, L. (George Washington Univ., Washington, DC 20052). *Diss Abstr Int [B]* 38(5): 2033B-2034B; 1977. (refs.)

**78-2257 Characterization of Early Simian Virus 40 Transcriptional Complexes: Late Transcription in the Absence of Detectable DNA Replication.** (Eng) Farnham, F. J. (Lab. DNA Tumor Viruses, NCI, NIH, Bethesda, MD 20014); Brown, M.; Khoury, G. *Proc Natl Acad Sci USA* 74(12): 5443-5447; 1977.

Sarkosyl extraction, which provides unprocessed RNA, is greatly enriched for virus-specific sequences in the supernatant fraction, was used to analyze early simian virus 40 (SV40) transcriptional complexes (VTC) and early virus-specific RNA. Under conditions such that viral DNA replication was undetectable, both early and late SV40 RNAs were synthesized, which indicates that viral DNA replication is not an absolute requirement for late transcription. Most of the early viral transcriptional activity could be solubilized, indicating that a substantial portion of this RNA is transcribed from free rather than integrated templates. Sedimentation analysis of the VTC resulted in the detection of separate peaks of activity; ie, there may be two distinct types of early SV40 templates. It is suggested that the transition from early to late SV40 transcription reflects a quantitative change rather than the initiation of a new process. At least



es, there is an increase in the frequency of late transcription relative to early transcription rather than a de novo initiation of late transcription. (30 refs.)

**78-2258 Nucleotide Sequence of the DNA Encoding the 5'-Terminal Sequences of Simian Virus 40 Late mRNA.** (Eng) Dhar, R. (NIH, Bethesda, MD, 20014); Reddy, V. B.; Weissman, S. M. *J Biol Chem* 253(2): 612-620; 1978.

The nucleotide sequence of the region of simian virus 40 (SV40) DNA complementary to the 5' end of messenger RNA for the viral structural protein VP2 of SV40 was determined by combined DNA and RNA sequence analyses. Comparison of the sequence with those found in polyadenylated RNA in the cytoplasm of infected cells showed that the transcript of sequences preceding the structural gene is more abundant than the transcript containing the codons for the protein. Between the abundant transcript and the less abundant transcript, there is a short sequence whose transcript was not detected. (34 refs)

**78-2259 5'-Terminal Sequences and Coding Region of Late Simian Virus 40 mRNAs Are Derived from Discontiguous Segments of the Viral Genome.** (Eng) Lavi, I. (Dept. Virology, Weizmann Inst. Science, Rehovot, Israel); Groner, Y. *Proc Natl Acad Sci USA* 74(12): 5323-5327; 1977.

The region of the simian virus 40 (SV40) genome complementary to the 5' end of the most abundant poly(A)-containing 16S and 16S messenger RNA's (mRNA's) was mapped by hybridization of double-labeled RNA <sup>3</sup>H methyl group and <sup>3</sup>H uridine to specific restriction endonuclease fragments of SV40 DNA. Chemical analysis of methylated residues indicated that a common "leader" sequence adjacent to the 5' terminus of both 19S and 16S mRNA is transcribed from DNA sequences located between 0.67 and 0.76 map unit. The estimated size of this leader RNA, which does not code for any known viral protein, is 170-200 nucleotides. Hybridization of intact RNA molecules with specific DNA fragments showed that sequences complementary to the leader region and coding portion of 16S mRNA are located in separate parts of the SV40 genome. Most of the models that may explain the biogenesis of these RNA molecules fall into two major classes: (1) the 19 and 16S RNA molecules are produced by the processing of a larger precursor RNA molecule; and (2) the 16S mRNA molecules are transcribed on a DNA template folded in such a way that the RNA polymerase will be able to transcribe nonadjacent sequences continuously. (17 refs.)

**78-2260 Sequence Arrangement of the 5' Ends of Simian Virus 40 16S and 19S mRNAs.** (Eng) Hsu, M. T. (Rockefeller Univ., New York, NY 10021); Ford, J. *Proc Natl Acad Sci USA* 74(11): 4982-4985; 1977.

Leader sequences were detected in 16S and 19S messenger RNA's (mRNA's) from simian virus 40 (SV40)-infected CV-1 cells by hybridizing them to SV40 DNA that had been digested with Endo-R-EcoRI4 restriction nuclease and subsequently treated with exonuclease III. The leader sequence for the 16S species appeared to be coded approx 0.2 genome length from the sequences coding for the 5' end (position 0.94) of the main body of the molecule. The leader at the 5' end of the 19S mRNA mapped at the same position, corresponding to map position 0.71-0.75. Electron microscopic observations were in agreement with these findings. (21 refs.)

**78-2261 Characterization of the 5'-Terminal Capped Structures of Late Simian Virus 40-specific mRNA.** (Eng) Haegeman, G. (Lab. Molecular Biology, State Univ. Ghent, 9000 Ghent, Belgium); Fiers, W. *J Virol* 25(3): 824-830; 1978.

The 5'-terminal capped structures of late simian virus 40 (SV40)-specific messenger RNA (mRNA) were isolated from SV40-infected CV<sub>1</sub> cells and characterized. The mRNA was degraded with RNase T<sub>2</sub> and bacterial alkaline phosphatase. The RNase-resistant material was fractionated by preparative electrophoresis on an agarose slab gel and further characterized with *Penicillium* nuclease and nucleotide pyrophosphatase. Two major 5' termini were identified in late SV40 mRNA; namely, 7-methyl Gppp 2',6-dimethyl ApUp and 7-methyl Gppp 2',6-dimethyl Ap 2'-methyl UpUp. Both 5' termini were present in unfractionated viral RNA as well as in the separated 16S and 19S species. As both caps differed only in secondary modification, it is possible that they were derived from the same site on the DNA. The relatively higher content of the latter capped structure in 16S mRNA may be related to its slower turnover rate. (32 refs)

**78-2262 Initiation Points for DNA Replication in Non-transformed and Simian Virus 40-transformed BALB/c 3T3 Cells.** (Eng) Oppenheim, A. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, Bethesda, MD 20014); Martin, R. G. *J Virol* 25(1): 450-452; 1978.

Nontransformed and simian virus-40 (SV40)-transformed BALB/c 3T3 cells were studied to determine the number of initiation points for DNA synthesis per unit length of DNA



in rapidly growing cells. DNA fiber radioautography allowed the direct visualization of replication forks that were radioactively labeled during a short pulse. The av distance between replication forks was estimated in both rapidly growing and starved cells. The av distance between initiation sites is twice the distance between forks. The number of initiation points per unit length of DNA is inversely proportional to the distance between initiation points. The geometric mean distances between replicating forks in SV40-transformed cells in depleted medium were 16  $\mu\text{m}$ ; in rapidly growing non-transformed cells they were 14  $\mu\text{m}$ , and in rapidly growing SV40-transformed cells they were 12  $\mu\text{m}$ . These results are compared with those using Chinese hamster lung cells. A long mean intertrack distance was observed in nontransformed 3T3 cells in isoleucine-depleted medium, and possible explanations are discussed. The geometric mean intertrack distance, and hence av replicon size, in rapidly growing SV40-transformed cells is less than that for rapidly growing non-transformed cells. Thus, there are more initiation points for DNA synthesis per unit length of DNA in randomly growing SV40-transformed than in nontransformed BALB/c 3T3 cells. (28 refs.)

- 78-2263 Differences in rRNA Metabolism of Primary and SV40-Transformed Human Fibroblasts.** (Eng) Liebhaber, S. A. (Depts. Microbiology and Immunology, Washington Univ. Sch. Medicine, St. Louis, MO, 63110); Wolf, S.; Schlessinger, D. *Cell* 13(1): 121-127; 1978.

Ribosomal RNA (rRNA) metabolism was compared in primary human diploid fibroblasts (WI-38) and in simian virus 40 (SV40)-transformed cultures derived from WI-38 (VA13 and SV-C52). In both actively growing and nondividing diploid fibroblasts, mature rRNA, labeled with  $^3\text{H}$ -uridine or  $^3\text{H}$ -methylmethionine, decayed with a half-life of 72 hr. In growing SV40-transformed cells, however, rRNA was stable, and it only began to show a half-life  $< 700$  hr as the cells reached max density. The net synthesis of rRNA was evaluated by measuring the transcription, processing, and wastage of pre-rRNA. The relative synthetic rates of 45S pre-rRNA increased by 50% or less in the transformed cells. In all cases, the processing rates were identical and little if any nuclear wastage was observed; all of the 45S pre-rRNA gave rise to mature 28S and 18S rRNA. In growing normal cells, the net level of RNA accumulation could be accounted for by the balance between the transcription of 45S pre-rRNA and cytoplasmic decay of 18S and 28S rRNA. In growing transformed cells, 18S and 28S rRNA were stable; therefore, the net formation of rRNA was determined only by the synthesis rate. The stabilization of rRNA in growing transformed fibroblasts does not seem to be a specific corollary of the faster growth rate of the transformed cells, since it is observed in transformed cell cultures but not in normal cell cultures doubling at similar rates. (27 refs)

- 78-2264 The Estimation and Characterisation of concanavalin A Receptors on the Surface of Non-transformed and SV-40 Transformed 3T3 Fibroblasts Using the Isoelectric Equilibrium Method.** (Eng) Sherbet, G. V. (Cancer Unit, Univ. Dept. Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, England); Lamm, M. S. *Exp Cell Biol* 46(1/2): 82-95; 1978.

A new method for estimating the number of concanavalin (Con A) receptors on the cell surface is presented that is based on assessing the effects of Con A on the isoelectric point of the cells. Untransformed BALB/c 3T3 fibroblasts (n3T3), 3T3 cells transformed by simian virus 40 (SV3T3), and cells treated with trypsin (t3T3) were used. In n3T3 cells there was a linear reduction in pI with Con A concentration up to 6.25  $\mu\text{g}/\text{ml}$ . No further change was observed at a concentration of 37.5  $\mu\text{g}/\text{ml}$  was reached, when further reductions occurred. It was thought that the linear decrease in pI represented Con A binding. The rate at which the pI increased was essentially the same for n3T3, t3T3, and SV3T3. At Con A concentrations of 50  $\mu\text{g}/\text{ml}$ , the three systems showed roughly the same amount of binding; saturation values for  $10^6$  cells were 5.4, 11.4, and 15.29  $\mu\text{g}$  for n3T3, t3T3, and SV3T3, respectively. The n3T3 cells possessed  $12.7 \times 10^3$  receptors/ $\text{Mm}^2$ ; values for t3T3 and SV3T3 cells were 36.6 and  $44.6 \times 10^3/\text{Mm}^2$ , respectively. There were three classes of receptors: K1, K2, and K3. The n3T3 cells appeared to possess K1, which Con A binds first. When these are saturated, binding of K2 and K3 at high concentrations occurs. K1 receptors were not detected on t3T3 and SV3T3 cells, and K2 receptors were not detected on n3T3 cells. It is suggested that K2 receptors appear as a result of trypsin treatment or viral transformation, indicating a conformational reorganization of membrane components. (42 refs.)

- 78-2265 Simian Virus 40 (SV40)-specific Proteins Associated with the Nuclear Matrix Isolated from Adenovirus Type 2-SV40 Hybrid Virus-infected HeLa Cells. Carry SV40 U-Antigen Determinants.** (Eng) Deppert, W. (Max Planck Inst. Biophysical Chemistry, D-3400 Goettingen, W. Germany). *J Virol* 26(1): 165-178; 1978.

The distribution of simian virus 40 (SV40)-specific proteins in nuclear subfractions of pulse-chase-labeled HeLa cells infected with nondefective adenovirus type 2 (Ad2)-SV40 hybrid viruses was analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis. The SV40-specific proteins of Ad2+ND1, Ad2+ND2, and Ad2+ND5 specifically associated with the nuclear matrix and were virtually absent from the high-salt nuclear extract. In Ad2+ND1-infected HeLa cells, the SV40-specific proteins with molecular weights of 64,000 (64K) and lower also specifically associated with the nuclear matrix. The SV40-specific 72K, 74K, and



teins were found both in the nuclear matrix and in the high-salt nuclear extract. Analyses of the nuclear matrices isolated from hybrid virus-infected cells by immunofluorescence microscopy showed that SV40 U-antigen-positive sera from SV40 tumor-bearing hamsters reacted with SV40-specific proteins integrated into nuclear matrices of HeLa cells infected by Ad2+ND1, Ad2+ND2, and Ad2+ND4, but not with nuclear matrices of HeLa cells infected by Ad2+ND5. This suggests that SV40-specific proteins of Ad2+ND1, Ad2+ND2, and Ad2+ND4 integrated into the nuclear matrix carry SV40 U-antigen determinants. (42 refs)

**78-2266 Cellular and Cell-free Synthesis of Simian Virus 40 T-Antigens in Permissive and Transformed Cells.** (Eng) Prives, C. (Virology Dept., Weizmann Institute, Rehovot, Israel); Gluzman, Y.; Winocour, E. *J Virol* 25: 587-595; 1978.

The synthesis of simian virus 40 (SV40) tumor (T) antigen was studied in permissive CV-1, BSC-1, and Vero monkey cells; transformed human, monkey, mouse, and hamster cells; and a transformed CV-1 line that is fully permissive to lytic reinfection. Messenger RNA (mRNA) from the SV40-infected monkey cell lines directed the cell-free synthesis of T-antigen polypeptides with mol wts of 90,000 and 17,000. However, there were considerable variations in the size and distribution of these T antigens in the different permissive and transformed cell lines. These variations did not correlate with the transformed or lytic state, since the distribution of T antigens was similar in transformed and superinfected transformed CV-1 cells. However, mouse SV3T3 cells contained a 94,000 T antigen in addition to the 90,000 antigen. Unlike the size variations in monkey cells, which were due to modification of the T-antigen polypeptides, the 94,000 SV3T3 T antigen resulted from an altered mRNA. This was evidenced by the appearance of the larger polypeptide in the cell-free products of SV3T3 mRNA. (21 refs)

**78-2267 Simian Virus 40 (SV40) Production from SV40-transformed Human Amnion Cells of Established Lines.** (Eng) Fogh, J. (Sloan-Kettering Inst. Cancer Res., 145 Boston Post Rd., Rye, NY, 10580); Loveless, J. *J Natl Cancer Inst* 60(4): 895-898; 1978.

Simian virus 40 (SV40) production was investigated in 16 lines of SV40-transformed amnion cells recovered from cultures established from six human amniotic membranes and maintained after the occurrence of crisis. Virus production continued in 2 lines for 18 mo, in 3 lines for 12 mo, and in 11 lines for 3 mo after recovery from crisis. Three lines became virus free in mo 1, 1 line in mo 2, 1 in mo 3, 1 in mo 4, and 1 between mo 6 and 11. The virus titers were relatively low;

inclusion body-containing cells were infrequent. In contrast, in most SV40-transformed human fibroblasts rescued from crisis, no infectious virus was demonstrated, although exceptions have been reported. Virus was produced after heterokaryon formation of cells of the virus-free amnion lines with CV-1 cells in the presence of inactivated Sendai virus, as observed for SV40-transformed human fibroblasts. During the crisis period, some of the SV40-transformed amnion cells produced substantial amounts of virus; titers decreased, however, during the later periods of crisis. The most pronounced decrease in titers was in cultures from which established lines were recovered. These findings indicate that cessation of virus production is not related to changes connected with recovery from crisis. (16 refs)

**78-2268 Expression of 'Early' and 'Late' Viral Functions in a Somatic Cell Hybrid Between a Mouse Cell and a Spontaneous Yielder SV40-transformed Chinese Hamster Cell.** (Eng) Suarez, H. G. (Institut de Recherches Scientifiques sur le Cancer, B.P. Nr. 8, F-94800 Villejuif, France); Lavialle, C.; Estrade, S.; Stevenet, J.; Cassingena, R. *Arch Virol* 56(1/2): 119-133; 1978.

A somatic hybrid cell line (Cl. 6d) derived from the fusion of mouse (3T3-4E) cells with simian virus 40 (SV40)-transformed Chinese hamster kidney (CHK/SVLP AG) cells, which produce the virus spontaneously, was studied. During the early passages, the hybrid cells underwent a rapid chromosome loss (35.6%), segregating chromosomes of both parental cells and preferentially losing hamster chromosomes. These changes were not constant, and after 31-47 passages, there was only a 5%-19% shift in total chromosome number. CHK/SVLP AG cells and the hybrid cells were always 100% SV40 tumor-antigen-positive. In the CHK/SVLP AG cells infectious SV40 DNA, virus capsid antigen, (VCA) and virus were detected regularly, but in the hybrid cells only infectious DNA was detected occasionally. This was not due to the loss of an essential Chinese hamster gene(s) or to the presence of an inhibiting mouse cell component(s). It is assumed that the resident viral genome could not be properly activated by the host cell. After superinfection with SV40 DNA, the hybrid cells, although capable of synthesizing SV40 VCA, were unable to clearly produce infectious virus. This suggests that SV40 maturation is dependent on a cellular function. (26 refs)

**78-2269 Solubilization and Characterization of Herpesvirus saimiri-induced Membrane Antigens.** (Eng) Qualtiere, L. F. (Dept. Microbiology, Mayo Foundation and Mayo Medical Sch., Rochester, MN, 55901); Pearson, G. R. *J Virol* 25(3): 852-859; 1978.

The isolation of membrane antigens (MA) from *Herpesvirus*



*saimiri* (HVS)-infected owl monkey cells is reported. Treatment of the cells by limited papain digestion removed the HSV-induced MA, as determined by membrane immunofluorescence and antibody-dependent lymphocyte cytotoxicity (ADLC). Soluble antigenically active HVSMA was detected by inhibition of ADLC and by the decreased binding of <sup>125</sup>I-labeled staphylococcus protein A to HVS-infected cells after absorption of an anti-MA-positive serum with papain extracts were sedimentable at 100,000 x g; this indicated that the released MA was heterogeneous in size. Preliminary investigations using gel chromatography revealed a major peak of MA with a mol wt between 20,000 and 50,000 daltons. (24 refs)

**78-2270 In Vitro Mitogenic Stimulation of Murine Spleen Cells by Herpes Simplex Virus.** (Eng)

Kirchner, H. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Darai, G.; Hirt, H. M.; Keyssner, K.; Munk, K. *J Immunol* 120(2): 641-645; 1978.

The mitogenic effect of herpes simplex virus type 1 [HSV-1 (WAL)] on spleen cell cultures from B6 mice was investigated. Cell-free supernatants recovered from HSV-1 (WAL)-infected mouse embryo fibroblasts had a stimulatory effect on DNA synthesis in B6 spleen cells. This activity was not lost by filtration and was enriched after centrifugation at 100,000 x g. However, the effect could be abolished by a specific rabbit anti-HSV serum and reversed by heating and UV light treatment. The stimulation of B6 spleen cells was superior in cultures containing a low percentage of phagocytic cells; pretreatment of the spleen cells by plastic adherence frequently enhanced the stimulation. Experiments with nylon columns, anti- $\theta$  antibody, and nude mice indicated that HSV acted as a B-cell mitogen. HSV-2 was also able to stimulate DNA synthesis in B6 spleen cells. A/J and DBA/2J mouse spleen cells pretreated by plastic adherence could also be stimulated by HSV-1 (WAL). Viral replication was not noted in B6 spleen cell cultures stimulated for DNA synthesis by HSV. Thus, HSV-induced stimulation of DNA synthesis in B cells could be abolished by virus inactivation. (15 refs)

**78-2271 Introduction of the Herpes Simplex Virus Thymidine Kinase Gene into Mouse Cells Using Virus DNA or Transformed Cell DNA.** (Eng) Minson, A. C.

(Div. Virology, Univ. Cambridge, Cambridge, England); Wildy, P.; Buchan, A.; Darby, G. *Cell* 13(3): 581-587; 1978.

The transformation of LMTK- cells, which lack thymidine kinase, into a kinase-positive phenotype using herpes simplex

virus (HSV) types 1 and 2 DNA is reported, and the properties of the transformed cells are described. Sheared DNA was used to transform the cells, and the enzyme function in the transformed cells was HSV-specific. Antiserum raised against HSV-1- or HSV-2-infected cells neutralized the kinase from the transformed cells. Each enzyme was also neutralized more by the homologous serum than by the heterologous serum. One of the cell lines was able to complement the functional defect found in two temperature-sensitive mutants of HSV-1; reversion of the cells to a thymidine kinase-negative phenotype resulted in the loss of this capability. The HSV thymidine kinase gene could also be introduced into LMTK- cells using DNA extracted from transformed cells. The efficiency of this procedure suggested that the state of virus DNA in transformed cells is different from that of DNA in virus particles. (24 refs)

**78-2272 Inhibition of Herpes Simplex Virus Type 1 Replication in Temperature Sensitive Cell Culture Mutants.** (Eng) Yanagi, K. (Dept. Biochemistry, New York Univ. Sch. Medicine, New York, NY, 10016); Talavera, Nishimoto, T.; Rush, M. G. *J Virol* 25(1): 42-50; 1978.

Herpes simplex virus type 1 DNA synthesis and infectious progeny production were studied in five temperature sensitive (*ts*) cell-cycle mutants of BHK-21 cells (*ts* A, *ts* 13, *ts* HJ-4, *ts* BTN-1, and *ts* BN-2). In wild-type BHK cells, the higher the multiplicity of infection (MOI), the earlier the onset and the greater the amount of viral DNA synthesized. At the nonpermissive temperature (39.5 C) and a low MOI [0.5 plaque-forming unit (PFU)/cell], viral DNA synthesis was inhibited completely in *ts* AF-8, *ts* 13, *ts* B, 1, and *ts* BN-2. However, at the nonpermissive temperature and at a high MOI (50 PFU/cell), viral DNA synthesis was inhibited in only *ts* BTN-1 and *ts* BN-2. Line *ts* HJ-4 supported viral DNA synthesis at 39.5 C regardless of MOI, though low MOI's yielded abnormally small amounts of viral DNA at both the permissive and nonpermissive temperatures. Another line, *ts*-422E, supported DNA synthesis to the same extent as the parental BHK line. Experiments involving shifts to the permissive temperature at least 3 hr postinfection to 33.5 C suggested that the defects in viral replication were not due to faulty absorption, penetration, or uncoating. Experiments involving shifts of infected cells from the nonpermissive temperature to 33.5 C revealed the reversible nature of the inhibition. (18 refs.)

**78-2273 Biochemical Transformation of Mouse Cells by Herpes Simplex Virus Types 1 and 2: Comparison of Different Methods for Inactivation of Viruses.** (Rapp, F. (Dept. Microbiology, Milton S. Eshelby Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033); Turner, N. *Arch Virol* 56(1/2): 77-87; 1977.



various methods of inactivating herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) were examined, and the virus isolates were compared in transformation assays. UV irradiation, photodynamic procedures, and heat all destroyed infectivity effectively. The ability to transform thymidine kinase-deficient cells biochemically to an enzyme-positive phenotype was retained after limited exposure to heat or UV, but it appeared to be destroyed by photodynamic methods using neutral red. The most rapid inactivation of transformation function appeared to result from treatment of the virus at 56°C; lower temperatures were less effective. The results indicate that the method of choice for transformation by HSV is UV irradiation, as this procedure yields the highest transformation frequencies observed with the isolates tested. Cell cultures developed by this procedure were virus-free but retained the ability to synthesize virus-specific antigens. (23 refs)

**78-2274 Integrated Viral DNA Sequences in Epstein-Barr Virus-converted Human Lymphoma Lines.**

(Eng) Andersson-Anvret, M. (Dept. Chemistry, Karolinska Inst., 104 01 Stockholm, Sweden); Lindahl, T. *J Virol* 25(3): 70-718; 1978.

Three human lymphoma-derived B-cell lines containing only a small amount of Epstein-Barr virus (EBV) were studied using neutral CsCl density gradient centrifugation, actinomycin D-CsCl gradient centrifugation, and Hirt fractionation. The EBV nuclear antigen-positive Ramos cell lines were obtained by infection of the cells with the P3HR-1 strain of EBV (AW-Ramos and EHRA-Ramos) or the B95-8 strain (Ramos/B95-8). AW-Ramos cells contained approx one EBV genome equivalent per cell, EHRA-Ramos had four, and Ramos/B95-8 had two. The evidence suggested that the EBV DNA was integrated into the cellular genome and was not present in nonintegrated cytoplasmic form. (38 refs)

**78-2275 Induction of Epstein-Barr Virus-associated Early Antigen in Different Lymphoid Cell Lines**

with Ultraviolet-irradiated P3HR-1 Virus. (Eng) Dalens, M. (Laboratoire de Bacteriologie-Virologie, Faculte de Medecine-Rangueil, 31500 Toulouse, France); Adams, A. *Virology* (2): 305-312; 1977.

The response of four human lymphoid cell lines, Raji, Daudi, Ramos, and Ramos, to infection with Epstein-Barr virus (EBV) that had been inactivated by varying doses of UV at 254 nm was determined. Raji and Daudi cell lines contain multiple copies of the EBV genome and the nuclear antigen is expressed in every cell; the former is a nonproducer and the latter is a producer. Infection of these two lines gave multihit survival curves for the expression of early antigen (EA). Infection of BJA and Ramos cells (which contain 0.3 EBV DNA/cell and do not express nuclear antigen) gave single-hit viral survival curves. The UV dose for 37%

survival of the EA-inducing potential of the virus preparation was 23 joules/m<sup>2</sup> when tested on the genome-negative lines and 300 joules/m<sup>2</sup> with the genome-positive lines. These findings are consistent with a requirement for an intact EBV genome for EA expression in genome-negative cells; resident viral genomes appear to function in the rescue of UV-inactivated superinfecting genomes in the genome-positive lines. (33 refs)

**78-2276 Scanning Electron Microscopy in the Analysis of Epstein-Barr Virus Containing Lymphoid Cells (Meeting Abstract).**

(Eng) Falcieri, E. (Istituto di Microscopia Elettronica Clinica, Universita di Bologna, Bologna, Italy); Zerbini, M. L. *J Submicrosc Cytol* 10(1): 126; 1978. (no refs)

**78-2277 Membrane Antigen Expression in Epstein-Barr Virus-infected Raji Cells in the Presence of Phosphonoacetic Acid.**

(Eng) Granlund, D. J. (Dept. Tumor Biology, Karolinska Inst., Stockholm, Sweden); Pearson, G. R. *Virology* 83(1): 217-220; 1977.

The effect of phosphonoacetic acid (PAA) on the expression of membrane antigen (MA) was investigated in Raji cells experimentally infected with Epstein-Barr virus (EBV). PAA concentrations ranging from 50 to 200 µg/ml had no adverse effects on the viability of superinfected Raji cells. Treatment with 50 µg/ml PAA did not significantly reduce viral capsid antigen (VCA), early antigen (EA), or MA expression. However, concentrations of 100 and 200 µg/ml reduced MA synthesis by 73% and 82%, respectively, and VCA synthesis by 91% and 96%, respectively; neither concentration affected EA expression. This indicated that MA synthesis was primarily a late event in the virus replication cycle. MA synthesis was reduced when 100 µg/ml PAA was present either during the entire 72-hr incubation period or only during the first 24 or 48 hr, but it was not inhibited when PAA was absent during the first 24-hr period. This suggested that viral DNA replication was required for synthesis of the MA complex. Monitoring of MA expression by the antibody-dependent lymphocyte cytotoxicity assay indicated essentially the same results. (19 refs)

**78-2278 Epstein-Barr Virus Infection of Cryopreserved Umbilical Cord Blood Lymphocytes.**

(Eng) Shope, T. C. (Dept. Pediatrics, Wayne State Univ. Sch. Medicine, 3901 Beaubien Blvd., Detroit, MI, 48201); Sell, M. K.; Smith, S. T.; Peterson, W. D.; Stulberg, C. S. *Proc Soc Exp Biol Med* 157(2): 326-329; 1978.

Human primary umbilical cord blood lymphocytes were



cryopreserved in the vapor phase of liquid nitrogen, and their sensitivity to Epstein-Barr virus (EBV) infection was examined. Frozen lymphocytes were rapidly thawed and resuspended in medium. Both the cryopreserved lymphocytes and fresh lymphocytes were exposed to serial tenfold dilutions of EBV and cultivated in combination with human placental fibroblast feeder layers. Cryopreserved lymphocytes were as sensitive to transformation by EBV as unfrozen, freshly cultured lymphocytes. Neither fresh nor cryopreserved lymphocytes were transformed unless EBV was added. Cell viability of recovered cryopreserved lymphocytes was 85%-88%. Cryopreserved lymphocytes from adult humans and cotton-top marmosets could also be transformed readily, and they supported EBV replication; in these cases, the infectability of cryopreserved and fresh cells was not compared. The method is a convenient time- and resource-saving technique, and the results indicate that, compared with autologous fresh cells, cryopreserved lymphocytes remain sensitive to infection and transformation by EBV. (20 refs)

- 78-2279 Identification of the Target Cells in Human B Lymphocytes for Transformation by Epstein-Barr Virus.** (Eng) Katsuki, T. (Dept. Microbiology, Kumamoto Univ. Medical Sch., Kumamoto, 860, Japan); Hinuma, Y.; Yamamoto, N.; Abo, T.; Kumagai, K. *Virology* 83(2): 287-294; 1977.

The type of lymphocyte that is the target for Epstein-Barr virus (EBV) transformation was investigated using blood from the umbilical cords of full-term newborns and from healthy adults. T and non-T (non-rosette-forming) cells were first separated, and the latter were divided into surface immunoglobulin (SIg)-carrying cells (B cells) and cells lacking SIg but carrying Fc receptors (null cells). Neither the T nor the null cells were susceptible to EBV transformation; B cells, however, were highly susceptible. The fraction size of transformable cells was determined by the growth curve procedure for transformed cells; direct membrane immunofluorescence with anti-IgM ( $\mu$ -specific) serum and polyvalent anti-Ig serum was used to determine the fractions of SIg and SIg(M) cells. The actual fraction of EBV target cells was nearly equal to that of SIg(M) B cells but not to that of the total SIg B cells. Lymphocyte preparations from 8 cord blood and 26 adult peripheral blood samples were examined for percentage of SIg B cells and for susceptibility to EBV transformation. EBV susceptibility and the fraction of SIg(M) B cells, but not of total SIg B cells, correlated nicely, suggesting that SIg(M)-bearing cells were probably the major target among B cells for EBV transformation. The relationship between EBV transformation and C' receptors was not determined. (21 refs)

- 78-2280 Radiobiological Inactivation of Epstein-Barr Virus.** (Eng) Henderson, E. (Dept. Pediatrics, Yale Univ. Sch. Medicine, New Haven, CT 06510); Heston, L.; Grogan, E.; Miller, G. *J Virol* 25(1): 51-59; 1978.

The transforming properties of UV- or x-ray-inactivated B95-8 strain Epstein-Barr virus were studied in three B lymphocyte lines and in primary human and marmoset lymphocytes. Radiation did not increase the transforming capacity of EBV. The x-ray dose needed for inactivation of EBV transformation (dose resulting in 37% survival, 60,000 rads) was similar to the dose required for inactivation of plaque formation by herpes simplex virus type 1 (Fischer strain). Although HSV is more sensitive than EBV to UV irradiation, this difference is most likely due to differences in the kinetics of mechanisms of repair of UV damage to the two viruses. A large part, or perhaps all, of the EBV genome may be needed to initiate transformation. The abilities of EBV to stimulate host cell DNA synthesis, to induce nuclear antigen, and to immortalize were inactivated in parallel. All clones of marmoset cells transformed by irradiated virus produced extracellular transforming virus. These findings suggest that the transforming and replicating abilities of the virus are inactivated together. The amounts of UV and x irradiation that inactivated transformation by B95-8 virus were less than the dose required to inactivate early antigen induction by nontransforming P<sub>3</sub>HR-1 strain of EBV. Based on radiobiological inactivation, 10%-50% of the genome was needed for early antigen induction. Inactivation of early antigen induction was influenced by the cells in which the assay was performed. It proceeded more rapidly in EBV genome-free cells than in the genome carrier Raji or in P<sub>3</sub>HR-1-converted EBV genome-free cells clone B<sub>1</sub>. These results indicate that the resident EBV genome participates in early antigen induction. Variation in the radiobiological killing of B95-8 and P<sub>3</sub>HR-1 EBV is not attributable to variations in the repair capacity of the host cells, since inactivation of HSV was the same in primary lymphocytes and in all lymphoid cell lines tested. (refs.)

- 78-2281 Autoradiographic Detection of Epstein-Barr Virus (EBV)-associated Early Antigen in a Variety of EBV DNA-containing Lymphoblastoid Cell Lines Previously Designated as Nonproducers.** (Eng) Moar, M. (Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm, Sweden); Siegfert, W.; Klein, G. *Intervirology* 9(6): 343; 1978.

A sensitive and specific method of antigen detection, which combines the <sup>125</sup>I-labeling of IgG prepared from the serum of a patient with high anti-early antigen (EA) titers plus autoradiography, was used to detect EA in Epstein-Barr virus (EBV) producer and nonproducer cells. Autoradiography and immunofluorescence were both effective in detecting EA in EBV producer cells, although the former appeared to be more sensitive than the latter. A variety of cell lines previously designated as nonproducers were then tested for their ability to react with various <sup>125</sup>O-IgG's. After immunofluorescence, a few lines were positive for EA but negative for capsid antigen (VCA). Most lines were negative for early antigen. After autoradiography, however, a much higher number of lines were positive with EA + VCA + <sup>125</sup>I-



ough a few were negative. EA was detected in only a low number of cells in each positive line. All nonproducer cells were negative with EA - VCA + <sup>125</sup>IgG. Iododeoxyuridine selection experiments were performed on nonproducer cells to determine if those that can be induced to produce EA are the same as those spontaneously expressing EA. The highly transformable lines were those that spontaneously expressed EA in a small percentage of the cells, suggesting a relationship between EA expression in both situations. These positive cell lines also contained multiple copies of the virus genome. (20 refs)

**282 Epstein-Barr Virus-associated Thymidine Kinase.** (Eng) Chen, S. T. (Cancer Res. Center, Department of Medicine, Univ. North Carolina at Chapel Hill, Chapel Hill, NC, 27514); Estes, J. E.; Huang, E. S.; Pagano, J. S. *J Natl Cancer Inst* 72(1): 203-208; 1978.

A thymidine kinase was identified that is distinguishable from both the adult and fetal kinases of the host cell by discontinuous electrophoresis on polyacrylamide gels and glycerol gradients. The enzyme was isolated following superinfection of Raji cells with 1 ml of medium containing  $8 \times 10^7$  infectious particles of Epstein-Barr virus. (23 refs)

**283 State of Epstein-Barr Virus DNA in an American Burkitt's Lymphoma Line: Brief Communication.** (Eng) Kolias, S. (Cancer Inst., Theagenion Memorial Hospital, Thessaloniki, Greece); Bjursell, G.; Adams, A.; Lindahl, B.; Klein, G. *J Natl Cancer Inst* 60(5): 991-994; 1978.

Epstein-Barr virus (EBV) genome was studied in a human lymphoma cell line (SU-Amb-2) positive for the EBV-associated nuclear antigen. The line was derived from a human American Burkitt's lymphoma. Hybridization experiments indicated that this line contained 58 EBV genome equivalents/cell. The DNA was present both as circular, integrated DNA molecules of viral genome length and as integrated sequences. An African Burkitt's lymphoma line was found to contain 59 EBV genome equivalents/cell; both integrated circular and integrated sequences were found in this line. The existence of an American Burkitt's lymphoma-derived cell line that carries episomal EBV DNA may permit a distinction to be made between geographic differences and other factors in studies of sequence arrangements of EBV DNA molecules from different sources. (10 refs)

**284 Persistent Infection and Viral Carrier State of a Human Lymphoblastoid Cell Line Infected with Mumps Virus Before Its Transformation.** (Eng) Giunta, L. (Sezione di Virologia, Laboratorio Analitico, Ospedale Policlinico I.N.R.C.A., Via Montagnola, 60100 Ancona, Italy); Boll, I. *Sieroter Milan* 56(5): 495-496; 1977.

A primary normal human lymphocyte cell culture was infected with mumps virus at a multiplicity of 0.005 TCID<sub>50</sub> per lymphocyte. A control culture was uninfected. Large clumps of lymphoblastoid cells appeared on the 18th day in the infected culture and on the 14th day in the control culture. One month following transformation, both cultures contained 0.2% Epstein-Barr virus (EBV)-positive cells, as detected by immunofluorescence. In the cell line infected with mumps virus, this virus was detected in the medium at a hemadsorption titer of  $10^2$  TCID<sub>50</sub>/ml. A fluorescent antibody assay indicated that 15%-18% of the cells contained mumps virus antigen. No mumps virus was detected in the control cell line. Since the resident latent EBV is the agent responsible for lymphoblastoid transformation, the mumps virus infection results in a superinfection. (6 refs)

**78-2285 Genetic Evidence for a Temperature-sensitive Lesion in the Adenovirus 7 Region of the PARA Genome.** (Eng) Estes, M. K. (Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX 77030); Butel, J. S. *Intervirology* 9(5): 261-275; 1978.

The replication of the defective adenovirus 7-simian virus 40 (Ad7-SV40) hybrid, PARA-Ad7, was investigated in permissive green monkey kidney cells. Both PARA-7 and the associated helper Ad7 grew to a high titer at the permissive temperature (33°C), but neither replicated well at the nonpermissive temperature (40.5°C). Complementation tests between the parental or transcapsidant PARA populations and SV40 or various Ad serotypes revealed that the temperature-sensitive (*ts*) lesion is located in the Ad region of the hybrid genome. Wild-type Ad7 and Ad21 (both subgroup B Ad's) were able to complement the replication of PARA, but Ad31 (from subgroup A) was not. Complementation was more efficient after the PARA genome was transcapsidated to the wild-type isolates of helper Ad than during multiple infections with the parental hybrid population. The SV40 function that complements the replication of human Ad's in simian cells is not expressed by PARA at the nonpermissive temperature. The *ts* lesion, however, does not affect the expression of several Ad and SV40 functions in PARA-transformed cells. These transformed cells maintain their characteristic morphology, continue to synthesize both SV40 and Ad tumor antigens, and express the ability to complement the replication of human Ad at the nonpermissive temperature. Although the exact nature of the mutated Ad7 gene product is unknown, heat-inactivation data suggest that it may be a structural protein. Other late functions might fail to be complemented, not because of the absence of the gene product, but because of its *ts* nature. (28 refs.)

**78-2286 Adenovirus Type 2 mRNA in Transformed Cells: Map Positions and Difference in Transport Time.** (Eng) Wilson, M. C. (Rockefeller Univ., New York, NY)



York, NY 10021); Sawicki, S. G.; Salditt-Georgieff, M.; Darnell, J. E. *J Virol* 25(1): 97-103; 1978.

Strain 8617 rat cells transformed by adenovirus type 2 (Ad2) produced two polyadenylic acid-terminated messenger RNA's (mRNA's) with approx coordinates 1.5-4.4 and 4.4-11.0 on the physical map of the Ad2 genome. These mRNA's were also formed early during lytic infection in addition to one or more smaller mRNA's from the 4.4-11.0 region. In transformed cells, the 1.5-4.4 mRNA appeared in the cell cytoplasm without detectable lag, but the 4.4-11.0 mRNA required at least 20 to 30 min for the max rate of accumulation. The need for metabolic studies of these RNA's is stressed. (26 refs.)

- 78-2287 **Evidence from UV Transcription Mapping that Late Adenovirus Type 2 mRNA Is Derived from a Large Precursor Molecule.** (Eng) Goldberg, S. (Rockefeller Univ., New York, NY, 10021); Nevins, J.; Darnell, J. E. *J Virol* 25(3): 806-810; 1978.

The source of late adenovirus type 2 messenger RNA (mRNA) was investigated in adenovirus-infected HeLa cells. UV irradiation, followed by labeling and hybridization, indicated that the labeling of cytoplasmic mRNA was depressed at least as much, if not more, than that of nuclear RNA complementary to the same fragment. All of the mRNA's complementary to DNA to the right of approx 42 on the genome had about the same UV target size as did the entire transcript of approx 28 kilobases from the right side of the genome. Poly(A)-containing cytoplasmic RNA from the 36.7-40.5 region was affected slightly less than the other mRNA's. Thus, the large, approx 28-kilobase transcript appears to be the obligatory precursor of cytoplasmic mRNA. The majority of the mRNA's derived from the large precursor apparently require the synthesis of the whole nuclear molecule. A UV-sensitive target necessary for proper processing of all the mRNA's may exist near the end of the transcription unit. (23 refs)

- 78-2288 **A Murine Oncornavirus Marker in Adenovirus 7-Transformed Mouse Cells.** (Eng) Merlitti, L. (Inst. Infectious Diseases, Università di Perugia, Perugia, Italy); Pauluzzi, S. *Tumori* 63(6): 519-523; 1977.

BALB/c mouse cells transformed by  $6 \times 10^7$  plaque-forming units of adenovirus 7/Hu 64-205/HEK were assayed for the presence of oncornavirus particles. The transformed cells (Ad7/BALB) produced tumors with a typical adenovirus morphology when they were transplanted, after 12 passages, into irradiated BALB/c mice. Sucrose density gradient of the virions from the Ad7/BALB cells demonstrated a large peak with a density of  $1.16 \text{ g/cm}^3$ . After 23 in vitro passages, the cells demonstrated cytoplasmic immunofluorescence indica-

tive of both p30 and T antigens in immunofluorescent assays. Electron microscopy failed to reveal any C-type particles. These findings indicate that the adenovirus genome is present in Ad7/BALB cells and that the morphology of the cells and the tumors they produce is under the control of this genome and not that of any C-type RNA viruses. (9 refs)

- 78-2289 **Characterization of DNA-Protein Complexes from Simian Adenovirus SA7.** (Eng) Esterhuysen, K. (Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX, 77030). *J Virol* 25(3): 917-922; 1978.

DNA-protein complexes isolated from purified simian adenovirus SA7 virions and lytically infected monkey kidney cells were compared. The DNA-protein complexes were isolated by the Hirt extraction method, and analysis of the complexes indicated that 88% of the viral DNA from purified virions and 75% of the DNA from infected cells fractionated into the Hirt supernatant. Complexes from both sources had similar properties when compared with respect to (1) sedimentation in sucrose gradient centrifugation, (2) configuration by electron microscopy, and (3) susceptibility to a variety of treatments by electron microscopy and electrophoresis in agarose gels. These complexes may play a role in adenovirus DNA replication. (29 refs)

- 78-2290 **Abortive and Transforming Infection of Rat Cell Line 3Y1 by Adenovirus Type 12.** (Eng) Hama, S. (Dept. Virology, Tottori Univ. Sch. Medicine, Yonago 683, Japan); Kimura, G. *J Virol* 25(3): 907-912; 1978.

The mechanism of transformation of 3Y1 rat cells by human adenovirus type 12 (Ad12) was investigated. Ad12 under both abortive and transforming infection in these cells. Transformation rate was directly proportional to the dose of input virus within the range of multiplicities of infection of 3-100 plaque-forming units/cell. The transformation frequency was greatly reduced by pretreatment of the virus with antibody prepared against purified Ad12 virions. (13 refs)

- 78-2291 **Induction of Intracisternal Type A Particles by 5-Bromo-2'-deoxyuridine in Rat Hepatoma Cells.** (Eng) Weber, H. W. (Dept. Biochemistry, Univ. of Southern California, Sch. Medicine, Los Angeles, CA, 90089); Geddes, A.; Stellwagen, R. H. *J Natl Cancer Inst* 60(4): 923; 1978.

The effects of 5-bromo-2'-deoxyuridine (BUdR:  $10^{-4}$  to  $10^{-6} \text{ M}$ ) on hepatoma tissue culture (HTC) cells were determined by electron microscopically. Untreated cultures had low



intracisternal A-type particles (IAP) and C-type viruses. C exposure to either concentration of BUdR caused a > fold increase in the number of IAP. The number of IAP increased after only 2 days of growth in  $10^{-5}$  M BUdR, but 5 days of growth in  $10^{-4}$  M BUdR were necessary to observe increase. A 2-day pulse of  $10^{-4}$  M BUdR was also sufficient to cause an increase in A-type particles, provided the cells were continued in culture for another 2 days. However, if C cultures were grown in  $10^{-4}$  M BUdR for only 1 day, increase in IAP occurred. An increase in C-type viruses was not observed at either concentration, as determined by a reverse transcriptase assay and an RNA probe. These findings support the idea that IAP and C-type particles are different. (29 refs)

**2292 Expression of Type C Virus p30 in Mouse Cells Infected with Herpes Simplex Virus. (Eng)**

Compar, B. (Lab. DNA Tumor Viruses, NCI, NIH, Bethesda, MD, 20014); Stephenson, J. R.; Boyd, A.; Derge, J. G.; Brown, A.; Oroszlan, S. *Virology* 83(2): 438-443; 1977.

The expression of C-type virus p30 in BALB/c and NIH Swiss mouse cells infected with live or UV-irradiated herpes simplex virus (HSV) types 1 and 2 was investigated to determine whether C-type virus activation could be detected by procedures that did not require synthesis of infectious virions. BALB/c cells neither immunofluorescence nor radioimmunoassay procedures revealed enhanced expression of p30; however, activation of C-type virus in UV-HSV-infected cells was readily demonstrated at low frequencies (approx  $10^{-4}$ ) by infectious center assay. Although immunofluorescent staining with rabbit anti-murine leukemia virus p30 serum was observed in mouse cells productively infected with HSV or infected with UV-HSV, it was nonspecific. No evidence of activation of C-type virus was obtained in NIH Swiss mouse cells infected with UV-HSV. It is concluded that the activation of C-type virus in UV-HSV-infected BALB/c cells does not occur in significantly more cells than those detected by infectious center assay. (12 refs)

**2293 Endogenous Mink (*Mustela vison*) Type C Virus Isolated from Sarcoma Virus-transformed Mink Cells. (Eng)**

Sherr, C. J. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20014); Benveniste, R. E.; Todaro, G. *J Virol* 25(3): 738-749; 1978.

C-type virus stock (PP-1R), isolated by cocultivating bann (*Papio papio*) cells with Aleutian mink (*Mustela vison*) cells transformed by Kirsten sarcoma virus (line 64J1), was isolated and characterized. End point-diluted stocks of PP-1R have been obtained that are free of focus-forming activity and are both Kirsten sarcoma and primate C-type viral sequences. Nucleic acid hybridization indicated that the cloned virus (MiLV) is an endogenous, genetically transmitted virus

of the mink. It replicates in canine, feline, and 64J1 mink cells, but not in an untransformed mink cell line. Multiple viral gene copies can be detected in the DNA of normal mink cells in culture and in normal mink tissues; related endogenous viral genes are also detected in several related *Mustela* species. The virus codes for a p30 protein closely related antigenically to that of feline leukemia virus, but it contains p15 and p12 proteins that are antigenically distinct. The mink cell line, Mv1Lu, and its Kirsten sarcoma-transformed derivative, 64J1, express relatively low levels of C-type viral RNA related to MiLV and normally do not produce detectable levels of MiLV p30 protein or complete, infectious viral particles. Infection of sarcoma virus-transformed mink cells with baboon C-type virus, however, resulted in the synthesis and packaging of mink viral RNA and p30 antigen in extracellular virions. (52 refs)

**78-2294 Characterization of the C-type Virus Produced In Vitro by MOPC-21 BALB/c Myeloma. (Eng)**

Krueger, R. G. (Lab., Molecular Oncology, Christ Hosp. Inst. Medical Res., 2141 Auburn Ave., Cincinnati, OH 45219). *J Gen Virol* 37(3): 475-485; 1977.

Studies of the C-type virus produced by a clone of MOPC-21 BALB/c myeloma cells [MO<sub>21</sub>-murine myeloma associated virus (MuMAV)] were performed to determine if this virus is similar to FL<sub>1</sub>-MuMAV produced by a clone of the FLOPC-1 line of BALB/c myeloma. Isopycnic gradient centrifugation indicated that both virus particles were extremely unstable, their enzymatic activity of virus RNA-dependent DNA polymerase was similar, they had similar antigenicity and SC syncytium-inducing activity, the endogenous RNA of both viruses contained polyadenosine tracts of a similar length, and they were NB-tropic in productive infection of BALB/3T3 and NIH/3T3 cells. RNA of MO<sub>21</sub>-MuMAV contained more high mol wt RNA species than FL<sub>1</sub>-MuMAV RNA and the former did not infect normal rat kidney cells as efficiently as the latter. Other studies indicated that MO<sub>21</sub>-MuMAV has dual tropism. These findings suggest that different BALB/c myelomas produce C-type viruses that are similar but not necessarily identical. (25 refs.)

**78-2295 Type-C Oncovirus Isolate from Human Leukemic Bone Marrow: Further In Vitro and In Vivo Characterization. (Eng)**

Nooter, K. (Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk, ZH, Netherlands); Overdevest, J.; Dubbes, R.; Koch, G.; Bentvelzen, P.; Zurcher, C.; Coolen, J.; Calafat, J. *Int J Cancer* 21(1): 27-34; 1978.

An attempt was made to detect and to isolate human C-type viruses by cocultivation techniques. The following lines were used: dog thymus (A7573), human rhabdomyosarcoma (A204), rabbit cornea (SIRC), and SIRC cells productively



infected with the human helper virus pseudotype of murine sarcoma virus (SKA21-3). SKA21-3 cells produced large amounts of transforming and nontransforming C-type viruses, and the high production was maintained for several months with passage. Transformation could be prevented by preincubation of the viral inoculum with a goat antiserum against autologous cells transformed by woolly monkey sarcoma virus. The murine sarcoma virus genome could be eliminated from SKA21-3 virus by inoculating high virus dilutions with A204 cells, which also increased the production of a virus designated A204(SKA). Both SKA21-3 and A204(SKA) cells possessed antigens closely related to those of woolly monkey sarcoma-leukemia type-C oncovirus. Injection of  $2.5 \times 10^6$  SKA21-3 cells sc into BALB/c mice produced no signs of disease, but the same inoculum in WAG/Rij rats resulted in fibrohistiocytic sarcomas in 20/20 animals. Five of the rats also exhibited generalized lymphosarcoma. Injection of the same dose of A204(SKA) cells into BALB/c mice had no effect, but inoculation into WAG/Rij rats resulted in lymphoblastic lymphosarcomas in 3/4 animals; no fibrohistiocytic tumors were noted, however. Uninfected SIRC or A204 cells had no tumorigenic ability. (24 refs.)

**78-2296 Serological Characterization of a Putative Human C-Type Oncovirus by Means of the Sepharose Bead Immunofluorescence Assay.** (Eng.) Koch, G. (Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk, Netherlands); Nooter, K.; Bentvelzen, P.; Haaijman, J. J. *Eur J Cancer* 13(12): 1397-1403; 1977.

Serological studies were performed in cultures of SKA21-3 rabbit cornea cells that were transformed by a murine sarcoma virus pseudotype with a presumably human derived C-type oncovirus as helper. A Sepharose bead immunofluorescence assay revealed that these cells produced abundant amounts of proteins related to the p28 protein of simian sarcoma virus (55V) but not the p30 protein of murine leukemia virus. Approx 1 mg of SSV related proteins was present per milliliter of culture fluid. When lymph node cells from a rat with an SKA21-3-induced sarcoma were cocultivated with canine A7573 cells, the culture produced high amounts of C-type oncoviruses. There were 524 nanograms (ng) of SSV-related proteins per milliliter of culture fluid. The same result was observed when a leukemic lymph node from a rat inoculated with the presumed human virus, free of murine sarcoma, was cocultured with the human A204 line. There were approx 425 ng of SSV-related proteins per milliliter of culture fluid. (14 refs.)

**78-2297 Transformation of Human Embryo Cells with the Use of Cell-free Extracts of a Human Rhabdomyosarcoma Cell Line (HUS-2).** (Eng.) Cook, B. (Dept. Anatomy, Coll. Health Sciences and Hosp., Univ. Kansas

Medical Center, 39th St. and Rainbow Blvd., Kansas City, KS, 66103); O'Sullivan, F.; Leung, J.; Morse, P.; Graham, B.; Chapman, A. L. *J Natl Cancer Inst* 60(5): 979-984; 1977.

The transformation of human embryonic HUE-20 fibroblasts by cell-free extracts of the human rhabdomyosarcoma HUS-2 cell line is reported. The transformation included morphologic alteration, karyotypic change, and an increase in cell longevity. RNA-dependent DNA polymerase activity in the particle with a specific gravity of  $1.16 \text{ g/cm}^3$  indicated the presence of an RNA C-type virus. Evidence also suggests that the known mammalian C-type viruses, routine cytopathic effect-inducing viruses, or mycoplasma were not the agents responsible for the transformation. That both the donor and the converted (HUE-T) cell lines cross-reacted with anti-HUS-2 prepared against HUE-T indicated a common antigen arising in the process of conversion of HUS-2 cells to HUE-T cells. It is suggested that a defective virus, with an appropriate helper virus in low titer, could have caused this transformation. (26 refs.)

**78-2298 Interspecies Radioimmunoassay for the Major Structural Proteins of Primate Type-D Retroviruses.** (Eng.) Colcher, D. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Teramoto, Y. A.; Scheraga, J. *Proc Natl Acad Sci USA* 74(12): 5739-5743; 1977.

A competition radioimmunoassay was developed in which D-type retroviruses from three primate species (rhesus, baboon, and squirrel monkeys) compete. The assay uses the major structural protein (36,000 daltons, p36) of the endogenous squirrel monkey retrovirus (SMRV) and antisera directed against the major structural protein (27,000 dalton, p27) of the Mason-Pfizer monkey virus (MPMV) isolated from rhesus monkeys. Purified preparations of both viruses grown in heterologous cells, as well as extracts of heterologous cells infected with SMRV or MPMV, competed completely in the assay. Addition of an endogenous virus of the langur monkey also resulted in complete blocking. No blocking was observed following the addition of three different baboon C-type isolates, simian sarcoma virus, gibbon virus, and a variety of other C- and B-type retroviruses (murine mammary tumor virus, murine leukemia virus, feline leukemia virus, myeloblastosis virus, etc.). One explanation for the complete blocking by MPMV and SMRV may be the presence of highly conserved antigenic determinants shared by a wide range of diverged primates that contain D-type retroviruses. These results indicate that an interspecies assay has been developed that recognizes D-type retroviruses from both Old World monkey (rhesus and langur) and New World monkey (squirrel) species. (37 refs.)

**78-2299 Tumor Antigen(s) in Cells Productively Infected by Wild-type Polyoma Virus and Mutant**



(Eng) Schaffhausen, B. S. (Dept. Pathology, Harvard Med. Sch., Boston, MA, 02115); Silver, J. E.; Benjamin, L. *Proc Natl Acad Sci USA* 75(1): 79-83; 1978.

The reaction of antipolyoma tumor (T) antiserum with mouse kidney cells productively infected with wild-type polyoma virus yielded a major polypeptide with a mol wt estimated 100,000 by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and at 81,000 by guanidine-Sepharose chromatography. The latter is considered to be the more reliable estimate. Cells infected by NG-18, an *hr-t* deletion mutant, produced a peptide that behaved identically to both wild-type species in the electrophoretic and chromatographic procedures. Furthermore, partial proteolytic digestion of mutant and wild-type 100,000 T antigen products revealed the two antigens to be highly similar, if not identical. Immunoprecipitates from wild-type infected cells showed four bands in addition to the 100,000 band; these had apparent mol wt 63,000, 56,000, 36,000, and 22,000 by sodium dodecyl sulfate-polyacrylamide gel electrophoresis; the 56,000 and 36,000 species were phosphorylated. All four of these lower mol wt bands were absent or drastically reduced in the immunoprecipitates from NG-18-infected cells. (35 refs)

78-2300 **Endogenous New World Primate Retrovirus: Interspecies Antigenic Determinants Shared with the Major Structural Protein of Type-D RNA Viruses of Old World Monkeys.** (Eng) Hino, S. (NCI, Bethesda, MD 20814); Tronick, S. R.; Heberling, R. L.; Kalter, S. S.; Hellman, A.; Aaronson, S. A. *Proc Natl Acad Sci USA* 74(12): 3457-3458; 1977.

A retrovirus recently isolated from the squirrel monkey (SMRV) was characterized biochemically and immunologically to determine its origin and genetic relationship to known primate retroviruses. Molecular hybridization studies demonstrated that the SMRV is endogenous to this New World primate, but it lacks detectable nucleotide sequence homology with cellular DNA's of representative Old World primates or with the genomes of previously isolated Old World primate retroviruses. The 35,000-dalton major structural protein (p35) of SMRV was purified and shown to possess antigenic determinants distinct from those of known retroviruses. SMRV failed to compete in a broadly reactive immunoassay that detects the p30 proteins of known mammalian C-type viruses. However, immunologic cross-reactivity was demonstrated between SMRV p35 and the major structural protein (p26) of Mason-Pfizer monkey virus (MPMV), a prototype D-type retrovirus of Old World monkeys. These findings support the concept that SMRV and MPMV are evolutionarily related, and they raise the possibility that a progenitor of D-type retroviruses became genetically associated with primates early in their evolution. The interspecies radioimmunoassay used can detect shared antigens of primate D-type viruses, and it may be valuable in the

search for evidence of endogenous retrovirus expression in man. (46 refs.)

78-2301 **Primate Retroviruses: Immunological Cross-reactivity Between Major Structural Proteins of New and Old World Primate Virus Isolates.** (Eng) Devare, S. G. (Viral Genetics Section, Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014); Arthur, L. O.; Fine, D. L.; Stephenson, J. R. *J Virol* 25(3): 797-805; 1978.

The major 35,000-dalton internal antigen (p35) of the squirrel monkey retrovirus (SMRV; New World) was isolated and partially characterized. Immunological analysis of SMRV p35 led to the demonstration of antigenic determinants common to SMRV and the Mason-Pfizer monkey virus (MPMV; Old World). A broadly reactive competition immunoassay was developed utilizing antiserum to MPMV to precipitate <sup>125</sup>I-labeled SMRV p35. Although the major structural proteins of MPMV and SMRV competed with equal efficiency in this assay, B-type and C-type oncornavirus proteins lacked detectable reactivity. Antibodies reactive with the major structural proteins of both MPMV and SMRV were observed in sera of several normal rhesus monkeys (Old World) with known prior exposure to MPMV-infected animals. These findings demonstrate the ability of sera from naturally immunized primates to recognize broadly reactive interspecies antigenic determinants shared by the major structural proteins of D-type oncornaviruses, and they suggest a possible horizontal transmission of MPMV among rhesus monkeys. Although sera from a number of squirrel monkeys contained antibody to SMRV p35, the possibility that this latter reactivity was due to endogenous virus activation rather than horizontal transmission cannot be ruled out. (35 refs)

78-2302 **Importance of Initiation Factor Preparations in the Translation of Reovirus and Globin mRNAs Lacking a 5'-Terminal 7-Methylguanosine.** (Eng) Held, W. A. (Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY 14263); West, K.; Gallagher, J. F. *J Biol Chem* 252(23): 8489-8497; 1977.

Messenger RNA's (mRNA's) lacking a 5'-terminal 7-methylguanosine are translated in vitro with optimal concentrations of reticulocyte initiation factor preparations but not with optimal concentrations of ascites initiation factor or suboptimal concentrations of reticulocyte initiation factor. At optimal concentrations of reticulocyte initiation factors, mRNA with a 5'-terminal 7-methylguanosine is preferentially translated in the presence of mRNA, which lacks a "cap". Thus, 5'-terminal 7-methylguanosine has a facilitatory rather than obligatory role in translation. (23 refs.)



**78-2303 Brain Tumors in Owl Monkeys Inoculated with JC Virus from a Patient with PML (Meeting Abstract).** (Eng) London, W. T. (Bethesda, MD); Houff, S. A.; Madden, D. L.; Fuccillo, D. A.; Gravell, M.; Sever, J. L.; Padgett, B. L.; Zurhein, G. M.; Walker, D. L. *Neurology (Minneapolis)* 28(4): 370; 1978. (no refs)

**78-2304 Detection of Viral-like Cores from the Urine of Patients with Genito-Urinary Malignancies.** (Eng) Cuatrecasas, W. (P. O. Box 1666, Idaho Falls, ID, 83401); Cheung, C. H.; Sy, F. *Cancer* 41(2): 706-711; 1978.

Urine samples from 18 patients with prostatic, bladder, or urethral cancer and, as controls, from 3 patients with benign prostatic hypertrophy and from 4 normal persons were examined for the presence of viruslike cores. Approx half were preoperative cases and the other half postoperative. Of the 18 patients with malignancy, 15 had urine positive for virus-

like particles. None of the controls had a positive reaction. Labeled DNA probes synthesized from the core structure hybridized readily to their corresponding polysomal RNA but not to control tissues. The densities of particles from the samples were 1.168 g/ml for bladder carcinoma and 1.169 g/ml for prostatic carcinoma, the same densities as those found in RNA tumor viruses. It is assumed that these particles originated from the tumor. It should be noted that the specimens from postoperative patients may give positive results for virus. (8 refs)

*See also:*

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## IMMUNOLOGY

**2305 Immunopathology of Follicular Lymphomas. A Model of B-Lymphocyte Homing.** (Eng) Arnke, R. (Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA, 94305); Levy, R. *N Engl J Med* 298(9): 486; 1978.

The monoclonality of follicular lymphoma (FL) was investigated in frozen tissue specimens (16 lymph nodes and 12 spleens from 22 patients) stained for  $\kappa$  and  $\lambda$  light chains by direct and indirect immunofluorescence. F(ab')<sub>2</sub> antibody fragments were used to avoid binding by Fc receptors. Specimens from 20/22 patients that showed staining of the lymphoma nodules for immunoglobulins also showed light-chain restriction; ie, they were monoclonal. Nine specimens stained exclusively for  $\kappa$  and 11 stained exclusively for  $\lambda$ . The nodules were usually surrounded by a normal, polyclonal population of B lymphocytes. Reactive lymphoid follicles were easily differentiated from lymphoma nodules on the basis of clonality. The FL cells showed the same light-chain restriction as normal B lymphocytes. In addition, like normal cells, the FL cells could produce more than one heavy chain (isotypes). All the lymphoma nodules in the same tissue or in multiple tissues in the same patient showed identical light-heavy-chain staining, even if different histologic subtypes were identified. Two lymph node regions from one patient were studied 9 mo apart (1 region was sampled 18 hr after splenectomy), and the lymphoma cells in both sites had identical light- and heavy-chain staining. Thus, the neoplastic cells of FL apparently arise from a single clone or a dominant clone that disseminates home to the center of lymphoid follicles, and may eventually displace the normal B lymphocytes in the mantle zones. (32 refs)

**2306 Rejection of a Transplantable Marek's Disease Lymphoma in Normal Versus Immunologically Deficient Chickens.** (Eng) Calnek, B. W. (Dept. Poultry and Aquatic Animal Medicine, New York State College of Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853); Fabricant, J.; Schat, K. A.; Murthy, K. K. *J Natl Cancer Inst* 60(3): 623-631; 1978.

Normal and immunosuppressed N-line chickens were challenged at 7 days of age with 0.1-0.5 ml of a 10%-20% homogenate of N cells containing Marek's disease virus (MDV). Immunosuppression was accomplished by various means: splenectomy (BX) on day 17 of incubation; neonatal thymectomy (TX, < 36 hr after hatching), intraabdominal injection of 6 mg cyclophosphamide (CP), TX + CP, BX + TX, or intraabdominal injection of 260 focus-forming units of GA-5

MDV 1 day after hatching. Tumors were generally apparent 6-7 days after injection, and they regressed rapidly after 14 days in most chicks. Another strain (P-line) had 20% the transplantation susceptibility of N-line chicks. Many birds in which the transplanted tumor regressed later developed visceral lymphomas. TX or CP had little effect on tumor rejection, but TX + CP prolonged the period before tumor rejection. BX enhanced transplant rejection; BX + TX mimicked the results of BX treatment, but the final incidence of MD was higher. Prior MD infection significantly delayed tumor rejection. The enhanced rejection in BX-treated animals could have been due to a blocking antibody, but the rejection pattern was not altered by repeated injections of sera from chicks with tumors or from chicks with tumors that regressed. Injections of convalescent sera from MDV-exposed birds enhanced transplant rejection in intact birds. (34 refs.)

**78-2307 Rabbit Antiserum Specific to Acute Leukemia Associated Antigen in Man (Meeting Abstract).** (Eng) Koshiba, H. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Minowada, J.; Han, T.; Higby, D. J.; Freeman, A. I.; Pressman, D. *Proc Am Assoc Cancer Res* 19: 109; 1978. (1 ref)

**78-2308 Serial Transplantation of Human B-Cell, T-Cell and Null-Cell Leukemic Cell Lines into Hamsters (Meeting Abstract).** (Eng) Miyoshi, I. (Dept. Medicine, Okayama Univ. Medical Sch., Okayama 700, Japan); Hiraki, S.; Nakamura, K.; Kimura, I. *Proc Am Assoc Cancer Res* 19: 12; 1978. (no refs)

**78-2309 Evidence that Tumor Antigens Enhance Tumor Growth In Vivo by Interacting with a Radiosensitive (Suppressor?) Cell Population.** (Eng) Hellstrom, K. E. (Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104); Hellstrom, I. *Proc Natl Acad Sci USA* 75(1): 436-440; 1978.

In BALB/c mice inoculated im with 10<sup>4</sup> cells of either of two 3-methylcholanthrene-induced syngeneic sarcomas, tumor growth was enhanced when the inoculum contained heavily x-irradiated (15,000 rads) cells from the same sarcoma. This enhancement did not occur in mice given 450 rads of total



body x-irradiation 1 day before tumor challenge. Tumor neutralization (Winn) tests showed that tumor cells irradiated in vitro enhanced tumor growth only in the presence of radiosensitive cells from the spleens of nonimmune and tumor-bearing mice. The spleen cells responsible for this effect were sensitive to anti-T serum and complement, indicating that they were T lymphocytes. The possibility that tumor antigens block tumor immunity by a suppressor cell mechanism is discussed. (28 refs.)

**78-2310 Enhancement of Metastasis Formation by Syngeneic Lymphocytes (Meeting Abstract).** (Eng)

Gersten, D. M. (Basic Res. Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Fidler, I. J. *Proc Am Assoc Cancer Res* 19: 6; 1978. (no refs)

**78-2311 Selective Inhibition and Stimulation of Xenogeneic Tumor Growth and Metastasis in Athymic Nude Mice (Meeting Abstract).** (Eng)

Kim, U. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Freedman, V. H.; Shin, S. I. *Proc Am Assoc Cancer Res* 19: 155; 1978. (no refs)

**78-2312 Effector and Suppressor Lymphoid Cells in Tumor Bearing Guinea Pigs (Meeting Abstract).**

(Eng) Berczi, I. (Dept. Immunology, Univ. Manitoba, Winnipeg, R3E 0W3, Canada); Schon, A. H. *Proc Am Assoc Cancer Res* 19: 187; 1978. (no refs)

**78-2313 Selective Depletion and Enrichment of Alloreactive Cytolytic Effector Lymphocytes Using Anti-Fluorescein Affinity Columns.** (Eng)

Singer, K. H. (Dept. Microbiology and Immunology, Div. Immunology, Duke Univ. Medical Center, Durham, NC, 27710); Johnston, C.; Amos, D. B.; Scott, D. W. *Cell Immunol* 36(1): 75-85; 1978.

A method was developed for the fractionation of alloreactive cytolytic effector lymphocytes (CL) by making use of their ability to bind fluoresceinated target cells and then separating the bound from unbound cells on anti fluorescein ( $\alpha$ ) affinity columns. C57BL leukemic EL4 cells were directly labeled with fluorescein isothiocyanate (FL-EL4) and centrifuged with CL, and the mixture was applied to a column of horse  $\alpha$ -FL antibody conjugated to Sepharose 4B. FL-EL4 and lymphocytes bound to them were retained on the column, but unbound lymphocytes were collected in a medium wash (passed cells). CL bound to FL-EL4 were eluted with EDTA. In a  $^{51}\text{Cr}$  release assay, passed cells were consistently depleted in cytolytic activity compared with unfractionated cells or

controls, reaching 100% depletion in some cases. Enrichment of cytolytic activity in eluted populations was frequently not invariably observed. The specificity of binding was investigated in reciprocal experiments using C57BL/6J effector cells raised against BALB/c lymphoma RL(male) 1. There was some depletion of cytolytic activity in fractions nonadherent to irrelevant targets, which indicated that cytolytically active cells were capable of binding irrelevant targets, but this depletion was not as great as that seen when CL were fractionated with the relevant target. In contrast to monolayer cell immunoabsorbents, contamination of fractions with adhering cells was consistently <5%. (45 refs)

**78-2314 Langerhans Cells as Target Cells in Mycobacterium Fungoides (Meeting Abstract).** (Eng)

Rovinsky, G. (Pathology Dept., Georgetown Univ., Washington, DC 20007); Lewis, M. G. *Proc Am Assoc Cancer Res* 19: 9; 1978. (no refs)

**78-2315 Studies on the Influence of the Metabolites of the Extraction Residue Tubercle Bacillus on Immunological Responsiveness of Mice.**

Effect of the Extraction Residue Tubercle Bacillus on Antibody Formation to a Soluble Protein and on Independent Antigen, Delayed Hypersensitivity Reaction in Sheep Erythrocytes and Numbers of Antigen-reactive Lymphoid Cells. (Eng.) Jacobs, D. M. (Dept. Microbiology, State Univ. New York at Buffalo, Buffalo, NY 14214); Pass, E.; Abraham, C.; Weiss, D. W. *J Med Sci* 14(1): 60-74; 1978.

The effects of pretreating BALB/c and C57Bl mice with methanol extraction residue (MER) fraction of tubercle bacilli on antibody formation to bovine  $\gamma$ -globulin (BGG), clearance of BGG from the circulation, formation of antigen-reactive cells (ARC) possessing  $\theta$ -antigen, delayed hypersensitivity to sheep RBC, and plaque-forming cell (PFC) response to trinitrophenylated lipopolysaccharide (TNP-LPS) were determined. Doses of 0.5 mg MER were administered intraperitoneally 14 and 3 days before sensitization with the various antigens. Adult mice that do not mount a primary antibody response to soluble BGG did so following pretreatment with MER and subsequent immunization with 100  $\mu\text{g}$  to 1 mg of antigen. Animals given MER in the first week of life responded to BGG immunization at 5 wk of age. Furthermore, when they were treated with MER and primed with BGG during the first week, they showed a higher response than untreated immunized controls to a later secondary sensitization. BGG was catabolized most rapidly in the first 24 hours following its introduction. MER heightened the ability of animals to produce both  $\theta$ - and  $\theta$ - ARC upon immunization with sheep RBC; the number of ARC in nonimmunized animals was increased only moderately. The delayed hypersensitivity response to sheep RBC was elevated in pretreated animals, especially when the specific immunization stim-



is limited. In contrast to the stimulatory action of MER T-cell-dependent or T-cell-mediated reactions, only a slight influence on reactivity to TNP-LPS was noted; the numbers of PFC increased moderately at the highest dose of antigen ( $2 \times 10^7$ ) tested. (42 refs.)

**78-2316 Regulation of Histocompatible Tumor Growth by Antiserum Prepared Against Subregions of MHC (Meeting Abstract).** (Eng) Williams, R. M. (Sidney R. Rober Cancer Inst., Boston, MA, 02115); Frelinger, J. A. *Proc Am Assoc Cancer Res* 19: 104; 1978. (no refs)

**78-2317 A T-Cell Antigen System of Chickens: Ly-4 and Marek's Disease.** (Eng) Fredericksen, T. L. (Dept. Microbiology, New York Univ. Sch. Medicine, New York, NY, 10016); Longenecker, B. M.; Pazderka, F.; Gilbour, D. G.; Ruth, R. F. *Immunogenetics* 5(6): 535-552; 1977.

Research was made for the lymphocyte antigens associated with resistance or susceptibility to the T-cell lymphoma induced by the herpesvirus of Marek's disease (MD) using MD-resistant line 6 (subline 1) and MD-susceptible line 7 (subline 1) chickens compatible at the major histocompatibility locus. Antisera were induced by reciprocal immunization and tested against lymphocytes of both lines. The lymphocytes were not agglutinated, immobilized, or lysed, but their ability to evoke graft-vs-host (GVH) splenomegaly was reduced. This inhibitory activity was line-specific, and the sera had a maximum limiting effect on GVH splenomegaly at a dilution of 1/50 and a minimum effect at 1/800 dilution. The differential limitation of GVH splenomegaly by a pair of alloantisera was used to identify antigens in the  $F_1$  and  $F_2$  generations. The segregation results established a locus, *Ly-4*, with two codominant alleles, *Ly-4a* and *Ly-4b*. *Ly-4* is distinct from the *A*, *B*, or *C* blood group loci and from the *Bu-1* locus determining B-cell antigens, but it may be linked to the *Th-1* locus determining T-cell antigens. Tentative evidence was obtained from comparisons of homozygous  $F_2$  and  $F_3$  progeny for an association of the *Ly-4* allele characteristic of the susceptible line with increased incidence of MD. (27 refs)

**78-2318 Gestational Choriocarcinoma: Cellular and Humoral Immunity to Paternal Antigens (Meeting Abstract).** (Eng) Shaw, A. R. (W. W. Cross Cancer Inst., Edmonton, Alberta, Canada T6G 1Z2); Kovithavongs, T. *Proc Am Assoc Cancer Res* 19: 405; 1978. (no refs)

**78-2319 Tumor Resistance Induced in a Syngeneic Host by Viable DTIC-Cells (Meeting Abstract).** (Eng) Nicolin, A. (Dept. Pharmacology, Sch. Medicine, Milan, Italy); Cavalli, M.; Marelli, O.; Goldin, A. *Proc Am Assoc Cancer Res* 19: 108; 1978. (no refs)

**78-2320 Cell Surface Markers of an Antigen Induced Murine Lymphoma (Meeting Abstract).** (Eng) Lanier, L. L. (Dept. Bacteriology and Immunology, Univ. North Carolina, Sch. Medicine, Chapel Hill, NC, 27514); Lynes, M.; Babcock, G.; Haughton, G. *Proc Am Assoc Cancer Res* 19: 118; 1978. (no refs)

**78-2321 TATA and Alien H-2 are Distinct Antigens on the Cell Surface of a Chemically Induced Fibrosarcoma (Meeting Abstract).** (Eng) Parmiani, G. (Div. Experimental Oncology A, Istituto Nazionale Tumori, Milan, Italy); Invernizzi, G.; Carbone, G. *Proc Am Assoc Cancer Res* 19: 55; 1978. (no refs)

**78-2322 Normal and Drug-mediated Transplantation Antigens (DMTA) of Drug-treated Murine Lymphomas (Meeting Abstract).** (Eng) Taramelli, D. (Inst. Pharmacology, Univ. Perugia, Perugia, Italy); Romani, L.; Fioretti, M. C.; Bonmassar, E.; Goldin, A. *Proc Am Assoc Cancer Res* 19: 147; 1978. (no refs)

**78-2323 Association of H-2 and Tumor Antigens on a Murine Lymphoma (Meeting Abstract).** (Eng) Callahan, G. N. (Scripps Clinic and Res. Foundation, La Jolla, CA, 92037); Allison, J. P.; Pellegrino, M. A.; Klein, J. *Proc Am Assoc Cancer Res* 19: 201; 1978. (no refs)

**78-2324 Presence of Foreign H-2 Like Antigenic Specificities on Reticulum Cell Sarcoma Cells Syngeneic to SJL Mice (Meeting Abstract).** (Eng) Fyfe, D. (Dept. Immunopathology, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH, 44106); Ponzio, N.; Finke, J. *Proc Am Assoc Cancer Res* 19: 154; 1978. (no refs)







## PATHOGENESIS

2326 **Kaposi's Sarcoma Associated with Dysimmunologic States.** (Fre) Amblard, P. (Clinique Dermatologique, C.H.U. de Grenoble, F 38700 La Tronche, France); Reymond, J. L.; Sotto, J. J.; Couderc, P. *Nouv Presse Med* (2): 122-123; 1978.

Two case reports are presented of immunological blood disorders associated with Kaposi's sarcoma. The first patient was a 6-yr-old woman with Waldenstrom's syndrome who developed Kaposi nodules of the lower extremities. A deficiency of lymphocytes had been observed in this patient 1 yr previously. The second patient was a 64-yr-old man who developed Kaposi nodules of the lower limbs after 15 yr of treatment with cortisone and chlorambucil for idiopathic thrombopenic purpura. (1 ref)

2327 **Light and Electron Microscopic Evaluation of the Histogenesis of Vascular Tumors.** (Rus) Gertsen, V. A. (P. A. Gertsen Oncological Res. Inst., Moscow, USSR); Iagubov, A. S.; Lavnikova, G. A. *Arkhl Patol* 39(12): 139; 1977.

Four human vascular tumors (2 hemangiopericytomas, 2 hemangioendotheliomas, 1 leiomyoma, and 1 leiomyosarcoma) were studied light and electron microscopically. The leiomyoma had the typical structure of a benign vascularized smooth muscle cell neoplasm with a large amount of dense microfibrils in the cytoplasm and well-developed nonspecific granules (ergastoplasm, mitochondria, and polyribosomes). The tumor was diagnosed as a differentiated smooth muscle tumor. The hemangioendotheliomas were characterized by numerous anastomosing vascular ducts and gaps lined with atypical endothelial cells. One of them was a pure hemangioendothelioma containing homogeneous cellular elements, and the other was polymorphic, containing transformed pericytes. The leiomyosarcoma consisted of bundles of elongated cells with rod-shaped or oval nuclei. One of the hemangiopericytomas consisted of round and polygonal cells packed densely between sinusoidal vessels; the other tumor contained oval and elongated cells that in certain places formed structures resembling the leiomyosarcoma. The first tumor was found to be polymorphic electron microscopically; it contained pericytes and endothelial cells. The findings indicate that many vascular neoplasms are polymorphic, containing two or even three cellular components of the vessel wall (endothelial cells, smooth muscle cells, and pericytes). (8 refs)

2328 **Hematopoietic Differentiation in Leukemic Myeloid X Erythroid Somatic Cell Hybrids**

(Meeting Abstract). (Eng) Ungerleider, R. S. (NIH, NCI, Bethesda, MD, 20014); Griffin, M. J.; Greenberger, J. S.; Moloney, W. C.; Deisseroth, A. B. *Proc Am Assoc Cancer Res* 19: 82; 1978. (no refs)

78-2329 **Detection of Cytochemical and Morphological Anomalies in "Preleukemia".** (Eng) Schmalzl, F. (Dept. Medicine, Univ. Innsbruck, Innsbruck, Austria); Konwalinka, G.; Michlmayr, G.; Abbrederis, K.; Braunsteiner, H. *Acta Haematol (Basel)* 59(1): 1-18; 1978.

A study was conducted to investigate whether the routine examination of blood and/or bone marrow smears by a series of cytochemical techniques can support the conjectural diagnosis of "preleukemia". Twenty-five patients, in whom preleukemia had been diagnosed on the basis of preliminary clinical information and cytochemical examination of blood and bone marrow smears, were followed. Seventeen of the 25 patients developed leukemia, 4 within 4 mo of diagnosis (imminent leukemia) and 13 within 4-25 mo following diagnosis (true preleukemia). Cytochemical defects indicative of preleukemia included quantitative differences of particular enzyme activities (peroxidase and neutral protease) in the polymorphonuclear neutrophils (PMN-N) of the same patients and coarse granules or clustered cytochemical reaction products. In some cases there was low WBC alkaline phosphatase activity. In monocytes, the atypical traits included the presence of granular deposits of glycogen as well as low and irregularly distributed naphthol-AS-D-acetate esterase. Increased numbers of weakly or strongly stained sideroblasts were also seen in preleukemia. In view of the current knowledge of the etiology, pathogenesis, and treatment of leukemia, the value of the diagnosis of preleukemia is a matter of debate. (48 refs.)

78-2330 **Biochemical and Morphological Analysis of Human Pre-Leukemic Splenic Tissue Culture** (Meeting Abstract). (Eng) Fuscaldo, A. A. (Cancer Inst., Hahnemann Medical Coll., Philadelphia, PA, 19102); Erlick, B. J.; Brodsky, I.; Fuscaldo, K. E. *Proc Am Assoc Cancer Res* 19: 99; 1978. (no refs)

78-2331 **Lymphocyte Studies in Familial Chronic Lymphatic Leukemia.** (Eng) Branda, R. F. (Dept. Medicine, Univ. Minnesota Hosps., Minneapolis, MN, 55455); Ackerman, S. K.; Handwerker, B. S.; Howe, R. B.; Douglas, S. D. *Am J Med* 64(3): 508-514; 1978.



Immunologic and morphologic studies were performed on peripheral blood mononuclear cells from a mother (89 yr old) and son (72 yr old) with chronic lymphocytic leukemia (CLL). The cells from both lacked detectable surface immunoglobulin and did not form sheep RBC rosettes; thus, neither are clearly B cell or T cell in origin. A significant percentage of cells from both patients formed EAC rosettes, but only a few were phagocytic. Peripheral blood mononuclear cells from both patients demonstrated diminished response to phytohemagglutinin, concanavalin A, and pokeweed mitogen. Cells from both patients showed low levels of cytotoxic activity against antibody-coated target cells. By light and electron microscopy, both patients' cells were small lymphocytes. Both patients had undetectable serum IgM and borderline low IgG, and they lacked skin test reactivity to four common antigens. Their clinical courses were also similar, with prolonged asymptomatic survival without therapy (10 and 18 yr since diagnosis) in the presence of marked lymphocytosis, mild anemia, and intermittent thrombocytopenia. These results suggest that the defect in this family may be an abnormality in maturation at a specific stage of lymphocyte development. (34 refs)

**78-2332 Lymphoblastic Conversion in Chronic Myelogenous Leukemia.** (Eng) Crist, W. M. (Children's Hosp., 1601 Sixth Ave. S., Birmingham, AL, 35233); Ragab, A. H.; Ducos, R. *Pediatrics* 61(4): 560-563; 1978.

An 11-yr-old boy who presented in a blast crisis with Philadelphia chromosome (Ph<sup>1</sup>)-positive chronic myelogenous leukemia (CML) had blast cells resembling lymphoblasts. Following induction of remission with vincristine, prednisone, and adriamycin, typical adult CML was observed. Clinical and laboratory studies suggested that a lymphoblast acceleration phase of childhood Ph<sup>1</sup>-positive CML does occur in some patients. (30 refs)

**78-2333 Morphology, Cytochemistry and Ultrastructure of the Lymphoblasts of T-Cell Acute Lymphoblastic Leukemia (T-ALL)** (Meeting Abstract). (Eng) McKenna, R. W. (Univ. Minnesota, Minneapolis, MN, 55455); Parkin, J.; Brunning, R. D. *Proc Am Assoc Cancer Res* 19: 139; 1978. (no refs)

**78-2334 Hairy Cell Leukemia. A Case with B-Lymphocyte Origin.** (Eng) Smith, W. I. (Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA 15261); Zidar, B. L.; Winkelstein, A.; Whiteside, T. L.; Shaddock, R. K.; Zeigler, Z.; Brietfeld, V.; Silverberg, J. H.; Rosenbach, L. M.; Rabin, B. S. *Am J Clin Pathol* 68(6): 778-786; 1977.

The results of studies on a 46-yr-old woman with hairy cell

leukemia of B-lymphocyte origin are reported. A high percentage of hairy cells examined immediately after isolation reacted with heavy chain-specific antisera; after a 24 hr incubation in serum-free medium, a decrease in reaction was noted for all classes except  $\gamma$  and  $\kappa$  chain. Examination of intracellular immunoglobulins indicated that they were predominantly  $\gamma$  chain; a decrease in the percent of  $\gamma$  chain was noted 3 wk after splenectomy. Cell suspensions from excised spleen and circulatory hairy cells had similar characteristics. A comparison of rosette formation using C<sub>3</sub>b receptors, C<sub>3</sub>d receptors, IgG receptors and RBC rosettes revealed 0, 52, 0, and 12% formation, respectively. At the time of initial presentation, both phytohemagglutinin and pokeweed mitogen responses were significantly reduced; repeat examination 1 mo after splenectomy showed normal mitogenic responses. The hairy cells were peroxidase-negative but did adhere to glass slides; lymphocytes from several patients with chronic lymphocytic leukemia also showed this property. Quantitative and qualitative phagocytic activity for latex particles and IgG- and C<sub>3</sub>-coated RBC was considerably decreased compared to values for normal monocytes. Medium conditioned by hairy cells failed to demonstrate stimulating factor on two occasions. Histochemical and microscopic studies revealed circulating mononuclear cells with scant to moderate cytoplasm, a round to slightly indented nucleus and irregular cytoplasmic processes. These cells showed a positive tartrate-resistant acid phosphatase stain. (32 refs.)

**78-2335 Experimental Simulation of Lymphogranulomatosis.** (Rus) Parakin, V. K. (Donetsk Agricultural Inst., USSR); Yermolaev, B. B.; Kotlyarov, N.; Silkina, L. F. *Veterinariia* (10): 71-73; 1977.

In an attempt to simulate the lymphogranulomatosis (LG) in horned animals, one merino ewe was inoculated with an extract of lymph nodes and spleen from a cow that died of lymphogranulomatosis (LG). For the first 3 yr after inoculation the sheep was in good health but then began to deteriorate. Autopsy showed marked enlargement of the inguinal and pelvic lymph nodes. Since the splenogram contained Beresovsky-Shternberg cells, diagnosis of LG was unequivocal. (no refs.)

**78-2336 Chromosome Findings in Effusions From Patients with Hodgkin's Disease.** (Eng) Hossain, D. K. (W. German Tumor Center, Medical Univ. of Essen, Tumor Res., Hufelandstrasse 55, 43 Essen I, W. Germany); Schmidt, C. G. *Int J Cancer* 21(2): 147-150; 1978.

Pleural and/or peritoneal effusion cells from six patients with advanced Hodgkin's disease were subjected to chromosome analysis. No Hodgkin's or Reed-Sternberg cells could be identified cytologically in 5/6 cases, but str



mosome anomalies of a clonal nature, including number of recurrent marker chromosomes, were seen in all effusions. Compared to chromosomal data from Hodgkin's diseased lymph nodes, the percentage of abnormal metaphases was considerably higher. Some of the marker chromosomes appeared to resemble those commonly seen in various other malignancies. The cells were neither typical T nor B cells, but they appear to be closely related to the pathogenesis of Hodgkin's disease and they could represent precursors of typical Hodgkin's cells. (11 refs)

-2337 **Sister Chromatid Exchange (SCE) in Lymphocytes from Patients with Malignant Lymphomas (Meeting Abstract).** (Eng) Bloomfield, C. D. (Univ. of Minnesota, Minneapolis, MN, 55455); Kurvink, K.; Levitt, J.; Cervenka, J. *Proc Am Assoc Cancer Res* 19: 126; 1978. (no refs)

-2338 **Karyotypic Abnormalities in Multiple Myeloma and Plasma Cell Leukemia (Meeting Abstract).** (Eng) Liang, W. (Franklin McLean Memorial Res. Inst., Univ. of Chicago, Chicago, IL, 60637). *Proc Am Assoc Cancer Res* 19: 212; 1978. (no refs)

-2339 **14q+ Marker Chromosomes in Multiple Myeloma and Plasma-Cell Leukaemia (Letter to the Editor).** (Eng) Liang, W. (Franklin McLean Memorial Res. Inst., Univ. of Chicago, Chicago, IL 60637); Rowley, J. D. *Cancer* 1(8055): 96; 1978.

22 patients with myelomatosis, an abnormal chromosome 14 with extra bands at the end of the long arm (14q+) was found in the bone marrow cells of 3 patients with multiple myeloma and in the peripheral WBC of 1 with plasma cell leukemia. (12 refs.)

-2340 **14q+ Marker Chromosomes in Malignant Lymphomas (Meeting Abstract).** (Eng) Fukuhara, S. (Univ. of Chicago Sch. of Medicine, Chicago, IL, 60637); Rowley, J. D. *Proc Am Assoc Cancer Res* 19: 73; 1978. (no refs)

-2341 **The Significance of the Philadelphia Chromosome in Acute Lymphoblastic Leukaemia: A Report of Two Cases.** (Eng) Gibbs, T. J. (Dept. of Clinical Haematology, Univ. of Liverpool, Nuffield Unit of Medical Genetics, Crown St., Liverpool L69 3BX, England); Wheeler,

M. V.; Bellingham, A. J.; Walker, S. *Br J Haematol* 37(4): 447-453; 1977.

Two adults with Philadelphia chromosome (Ph<sup>+</sup>)-positive acute lymphoblastic leukemia (ALL) are reported, both of which lost the Ph<sup>+</sup> chromosome during remission. In one patient, a 54-yr-old man, ALL remission continued, but classical Ph<sup>+</sup>-positive chronic granulocytic leukemia developed. In the second patient, a 20-yr-old woman, relapse of ALL occurred, and it was associated with the return of the Ph<sup>+</sup> chromosome. The findings suggest that the chromosome aberration occurred in a pluripotential stem cell, which in the first case proliferated along both a lymphoid cell line and a myeloid cell line. The importance of chromosome studies and surface marker characteristics as part of the initial investigation of cases of acute leukemia and during the course of the disease is clear. The results suggest that they may not only be diagnostic but also more sensitive markers of remission than the marrow morphology. (9 refs)

78-2342 **Mapping of Human Chromosomal Regions Related to Neoplasia: Evidence from Chromosome 1 and 17.** (Eng) Rowley, J. D. (Dept. of Medicine, Univ. of Chicago, Chicago, IL 60637). *Proc Natl Acad Sci USA* 74(12): 5729-5733; 1977.

Abnormalities in chromosomes 1 and 17 in the cells of patients with hematologic disorders were examined. In clonal aberrations leading to an excess or partial excess of chromosome 1, trisomy for bands 1q25-1q32 was observed in the myeloid cells from all of 34 patients who had disorders such as acute leukemia, polycythemia vera, and myelofibrosis. This consistent aberration in the long arm is not the result of a particularly fragile site in that region of the chromosome, because the break points in reciprocal translocations were almost exclusively in the short arm. Two consistent rearrangements were observed in chromosome 17, which produced either duplication of the entire long arm or a translocation of the distal portion of the long arm to chromosome 15. Because several different nonrandom chromosomal aberrations have been identified in patients with hematologic disorders, it is apparent that no single gene locus provides the mutant cells with a proliferative advantage. It may be significant that chromosomes carrying gene loci related to nucleic acid metabolism are more frequently involved in hematologic disorders (and other malignancies) than gene loci related to intermediary or carbohydrate metabolism. The known virus-human chromosome associations are also closely correlated with the chromosomes affected in hematologic disorders. (37 refs.)

78-2343 **Retinoblastoma and Subband Deletion of Chromosome 13.** (Eng) Yunis, J. J. (Medical Genetics Div., Dept. of Lab. Medicine and Pathology, Univ. of Minnesota Medical Sch., Box 198, Mayo Memorial Building,



Minneapolis, MN, 55455); Ramsay, N. *Am J Dis Child* 132(2): 161-163; 1978.

Chromosomal studies of two unrelated patients with retinoblastoma (an 8-mo-old boy and a 15-mo-old girl) revealed an interstitial deletion of the long arm of chromosome 13. The former patient showed several congenital defects, developmental retardation, and deletion of bands q14 and q21. The latter exhibited mild developmental delay, a few minor congenital defects, and a loss of approx half of band q14. The identification of two retinoblastoma patients with a common deletion of band q14 suggests that a relationship exists between the deletion and the tumor, although the exact role of the former in tumor development is not known. (17 refs)

**78-2344 The Association of Bronchial Carcinoid and Acromegaly: A Case Report.** (Eng) Baris, Y. I. (Div. Chest Diseases, Sch. Medicine, Hacettepe Univ., Ankara, Turkey); Artvinli, M. *Kanser* 7(1): 38-42; 1977.

A 32-yr-old woman who presented with a 4-yr duration of acromegalic symptoms was subsequently found to have a carcinoid-type bronchial adenoma. She had been admitted for hemoptysis 15 yr previously, but medical treatments and left artificial pneumothorax were ineffective. The pneumothorax led to collapse of the left lung. A diagnosis of tuberculosis was made. The tumor was finally discovered by bronchoscopy 15 yr later. Seven similar acromegaly/bronchial carcinoid cases have been found in the literature. Because of the ectopic secretion of active endocrine substances from these tumors and the endocrinelike structure of bronchial carcinoids, it is suggested that a common mechanism was involved in the pathogenesis of the acromegaly and the bronchial carcinoid. (17 refs)

**78-2345 Histochemical and Electron Microscopic Studies of Proliferation of Connective Tissue in Gastric Carcinoma. Part 2: Vascular Invasion of Gastric Carcinoma Related to the Proliferation of Connective Tissue.** (Jpn) Hanabusa, N. (First Dept. Surgery, Okayama Univ., Medical Sch., Shikada-cho, Okayama 700, Japan). *Okayama Igakkai Zasshi* 89(9/10): 1069-1081; 1977.

The relationship between vascular invasion by gastric carcinoma and connective tissue proliferation was studied in 102 resected cancers. Of the three types of vascular invasion that were identified, extraluminal and floating invasion were common in well-differentiated adenocarcinomas and extraluminal invasion was common in poorly differentiated adenocarcinomas. Invasion of lymph vessels was more prominent in the poorly differentiated tumors. Electron microscopic observations of connective tissue proliferation showed that the embolus and floating types of invasion were

more frequent than the extraluminal type in medullary carcinomas. Conversely, the extraluminal type predominated in scirrhous carcinomas. These findings indicate that the type of vascular invasion is influenced not only by tumor proliferation, but also by connective tissue proliferation. (27 refs)

**78-2346 Early Gastric Cancer at the Oral Margin of Duodenal Bulbar Ulcer. Report of a Case.** (Jpn) Tokunaga, O. (Dept. Pathology, Kurume Univ. Sch. Medicine, Kurume, Japan); Morimatsu, M.; Nakashima, Murashima, F.; Koba, K.; Jinnai, M.; Koganemaru, M. *J Cancer Clin* 23(14): 1351-1354; 1977.

A 66-yr-old man had a poorly differentiated adenocarcinoma at the proximal margin of a perforated duodenal ulcer. The ulcer had first been noticed 1 yr previously; however, a review of the patient's gastrointestinal tract x-rays over the past 10 yr revealed an abnormal lesion at the gastroduodenal junction of 3 yr duration. The cancer had originated from the gastric mucosa; there was no cancerous tissue in the duodenal mucosa at the distal margin of the ulcer. (7 refs.)

**78-2347 Epithelial Cell Kinetics in the Crypts of Familial Polyposis of Colon.** (Eng) Iwama, T. (Dept. Surgery, Tokyo Medical Dental Univ., Tokyo, Japan); Sugimura, J.; Sasaki, J. *Jpn J Surg* 7(4): 230-234; 1977.

Autoradiography was used to investigate epithelial cell kinetics in the uninvolved part of the rectal mucosa from nine patients with familial polyposis of the colon (FPC), six of their first-degree relatives, and six control patients. Biopsy specimens, taken from a site 10 cm proximal to the anus, were incubated for 2 hr in medium containing  $^3\text{H}$ -thymidine. The polyps of FPC were biopsied, one of which contained a carcinoma. In this carcinomatous polyp, all the surface cells incorporated  $^3\text{H}$ -thymidine; in the adenomatous polyps, incorporation occurred in the cells located in the upper part of or throughout the length of the crypts. In the normal rectal mucosa, the incorporation patterns differed between control specimens and those from FPC patients and relatives. In the controls, the proliferating zone was confined to the lower two-thirds of the crypt in all cases except one (from a patient with hemorrhoids). Six of the nine FPC specimens had crypts with an altered proliferating zone; i.e.,  $^3\text{H}$ -thymidine incorporation was observed in the upper one-third of the crypt, similar to the adenomatous polyps and to the specimens from the relatives. There were significant differences ( $p < 0.01$ ) in the incidence of altered kinetics between controls and FPC patients or their relatives, but not between the FPC patients and their relatives. It may be possible to detect latent FPC by autoradiography of the rectal mucosa. (11 refs)



8-2348 **Pentastomiasis and Cancer of the Colon.** (Eng) Bygbjerg, I. C. (Dept. Medicine, Hospital B.Z.O., Sona Bata, Bas-Zaire, Africa); Rask, M. P. *Trans Soc Trop Med Hyg* 72(1): 54-55; 1978.

50-yr-old man with cancer of the colon was found to have both *Entamoeba histolytica* and *Armillifer armillatus* infections. X-rays revealed that the tumor contained small calcified pentastomid nymphs, probably of *A. armillatus*. The tumor arose from the epithelium; no metastases were noted. This is the first known association of *A. armillatus* pentastomiasis and cancer of the colon. It is suggested that pentastomids may have some carcinogenic action. (8 refs)

8-2349 **Familial Polyposis of the Large Intestine and Gardner's Syndrome.** (Cze) Jirasek, V. (I. Interní Kliniky Fakulty Všeobecného Lékárství KU, U Nemocnice 2, Praha, Czechoslovakia); Chmel, J.; Balas, V.; Zboril, I. *Cesk Gastroenterol Vyz* 31(8): 539-548; 1977.

The results of studies of 14 patients with diffuse adenomatosis of the large intestine are presented. Thirteen patients were drawn from five families with a proved familial incidence of the disease; one case appeared to be solitary. Almost all patients had bone changes or soft tissue tumors consistent with the diagnosis of Gardner's syndrome; one had diffuse adenomatosis of the duodenum. These extraintestinal manifestations differed as to number, intensity, and combination in the different families. Endocraniosis, usually marked, was present in 12 patients; this is the first known association of this sign with Gardner's syndrome. Malignant change in adenomas occurred in three patients. Five patients were treated by total proctocolectomy, nine with colectomy, ileorectal anastomosis, and cauterization of rectal polyps. It is suggested that Gardner's syndrome and familial polyposis of the large intestine form a single nosological unit, with different degrees of expressiveness. (35 refs)

8-2350 **Chronic Pancreatitis and Cancer of the Pancreas.** (Cze) Herfort, K. (II. Vedecké Gastroenterologické Oddělení Fakulty Všeobecného Lékárství a Interní Oddělení Fakultní Polikliniky, 121 11 Prague 2, Czechoslovakia); Zeman, J. *Cesk Gastroenterol Vyz* 31(6): 663-666; 1977.

Of 151 patients with chronic pancreatitis followed for 5-15 yr, only 1 developed cancer. A literature review of 506 patients followed for 8-22 yr revealed only 8 more cases. Thus, the incidence of pancreatic cancer in this combined series was only 1.4%, less than that for the general population (2.2%-3.0%). These findings indicate that chronic pancreatitis is not a precancerous condition. (19 refs.)

78-2351 **Multiple Nodular Hyperplasia of the Liver Associated with Oral Contraceptives.** (Ger) Roschlau, G. (Pathologisches Institut, Fetscherstrasse 74, DDR-8019 Dresden, E. Germany). *Zentralbl Allg Pathol* 121(6): 517-521; 1977.

Multiple nodular hyperplasia (MNH) of the liver occurred in two women following oral contraceptive (OC) use. One 37-yr-old woman took Ovoston and Non-Ovlon from 1971 to 1973. She underwent surgery for cervical carcinoma in 1973. Laparotomy, performed for a planned cholecystectomy in 1976, revealed MNH of the liver. Another 34-yr-old woman took OC from 1969 to 1976. A hepatic tumor was resected in 1971. MNH with epithelioid cell granuloma of the septa was found in the left lobe of the liver in 1976. Anisokaryosis of the hepatocytes with an increased glycogen level in the nuclei and cytoplasm, focal ectasia of the sinusoids, and atrophy of the adjacent liver cells were found in the other lobe. The findings and literature data show a causal relationship between OC usage and MNH. The changes may be due to hypertrophy of the agranular endoplasmic reticulum of the hepatocytes as a result of enzyme induction under long-term use of OC. (16 refs.)

78-2352 **Mosaic Mice with Teratocarcinoma-derived Mutant Cells Deficient in Hypoxanthine Phosphoribosyltransferase.** (Eng) Dewey, M. J. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Martin, D. W.; Martin, G. R.; Mintz, B. *Proc Natl Acad Sci USA* 74(12): 5564-5568; 1977.

Mosaic mice with teratocarcinoma-derived mutant cells deficient in hypoxanthine phosphoribosyltransferase (HPRT) have been bred successfully as the initial step in a scheme to select in vitro for specific mutations in developmentally totipotent cells, so that the effects of a biochemically defined change can be followed in vivo. Mutagenized stem cells of a cultured mouse teratocarcinoma cell line were selected for resistance to the purine base analog 6-thioguanine. Cells of a resistant clone were completely deficient in HPRT activity, the same X-linked lesion that occurs in human Lesch-Nyhan disease. After microinjection into blastocysts of another genetic strain, the previously malignant cells participated in normal embryogenesis, and tumor-free, viable mosaic mice were obtained. Tumor cells were identified by strain markers in virtually all tissues of some mice. The mature function of those cells was evident from their tissue-specific products. Retention of the HPRT deficiency in the differentiated state was documented in mosaic tissues by the depressed specific activity of the enzyme and by the presence of unlabeled clones in autoradiographs of explanted cells incubated in <sup>3</sup>H-hypoxanthine. Some mosaic mice had mutant strain cells in only one or a few tissues. The tissue distribution of HPRT-deficient cells suggests that selection against them is particularly strong in the blood of mosaic mice, similar to human



heterozygotes. This phenotypic parallelism supports the expectation that afflicted F<sub>1</sub> male mice that might be obtained from mutant germ cells could serve as a model of the human disease. (30 refs.)

- 78-2353 Endocrine Studies in Testicular Tumor Patients With and Without Gynecomastia. A Report of 45 Cases.** (Eng) Stepanas, A. V. (Section Endocrinology, Dept. Medicine, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX 77030); Samaan, N. A.; Schultz, P. N.; Holoye, P. Y. *Cancer* 41(1): 369-376; 1978.

Serum levels of prolactin (PRL), human placental lactogen (hPL), the  $\beta$ -subunit of human chorionic gonadotropin ( $\beta$ hCG), testosterone (T), estrone (E<sub>1</sub>), and estradiol (E<sub>2</sub>) were measured by specific radioimmunoassays in 45 patients with testicular tumors. Forty-two patients had at least one abnormal hormone level. The most common abnormality was an elevated E<sub>1</sub> concentration (32/42 cases), which suggests a useful role for this hormone as a testicular tumor marker. The prognosis was poor in patients with embryonal carcinoma (16), teratocarcinoma (10), choriocarcinoma (8), gynecomastia (27), and particularly, in patients with galactorrhea (4). These groups had the highest incidence of hormonal abnormalities and the most extreme absolute values. Hormonal mechanisms were implicated in the development of gynecomastia and galactorrhea. PRL,  $\beta$ hCG, E<sub>1</sub> and E<sub>2</sub> levels were significantly correlated only in patients with gynecomastia, but not in those without it. In patients with galactorrhea, E<sub>1</sub>/T ratios were high. (22 refs.)

- 78-2354 Precursors of Endometrial Cancer.** (Eng) Sherman, A. I. (Dept. Obstetrics and Gynecology, Sinai Hosp. Detroit, Detroit, MI, 48235). *Isr J Med Sci* 14(3): 370-378; 1978.

Endometrial carcinogenesis is viewed as though an inductive stimulus initiated the neoplastic process in which the glandular response in its earliest phase is represented by minor hyperplastic changes. With persistent stimulation, the endometrium changes progressively to an endometrial cancer. By analogy to a suggestion that the entire range of premalignant cervical disease be referred to as cervical intraepithelial neoplasia, it is proposed that the endometrial counterpart be called intraepithelial carcinoma of the endometrium (ICE) and that it be subdivided into ICE I (adenomatous hyperplasia), ICE II (atypical adenomatous hyperplasia), and ICE III (carcinoma in situ). In a retrospective study of 201 patients with endometrial carcinoma (60 yr old or older), 72% had a diagnosis 2-10 yr earlier corresponding to one of the

precursor types ICE I, II, or III. Only 2% had cystic hyperplasia, and 18% showed proliferative endometrium. In another study, 73/197 women in the ICE I and II categories followed for 2-15 yr developed invasive cancer of the endometrium. This high association of subsequent development of endometrial carcinoma among the subjects with precursor types demonstrates a degree of correlation sufficient to label these lesions as true precursor lesions. (10 refs)

- 78-2355 Premalignant and Malignant Uterine Changes in Immunosuppressed Renal Transplant Recipients.** (Eng) Husslein, H. (II Universitat-Frauenklinik, Spitalgasse 23, 1090 Vienna, Austria); Breitenacker, G.; Tatra, J. *Acta Obstet Gynecol Scand* 57(1): 73-78; 1978.

Twenty-nine women, aged 13-50 yr, who had been renal transplant recipients 2-100 mo previously and had received posttransplantation immunosuppressive therapy were examined gynecologically. The cervical portio epithelium was normal in only 4 patients; 14 had iodine negative stainable areas; 6, ectopia; 5, a transformation zone; 4, leukoplakia; and 6, additional slight leukoplakia. Twenty-two women, one aged 32 who had received a kidney 24 mo previously and one aged 30 who had received a kidney 8 yr previously, were found to have dysplasia. A 48-yr-old woman who had received a kidney 20 mo previously had a well differentiated adenocarcinoma of the endometrium. These findings emphasize the need for regular gynecologic and cytologic examinations to detect early malignant uterine changes in patients on immunosuppressive therapy. (14 refs)

- 78-2356 Rokitansky-Kuster-Hauser Syndrome and Leiomyoma Uteri.** (Eng) Farber, M. (Dept. Obstetrics and Gynecology, New England Medical Center Hospital, 171 Harrison Ave., Boston, MA 02111); Stein, J.; Adashi, E. *Obstet Gynecol* 51(1, Suppl): 70s-71s; 1978.

The case report of a 23-yr-old woman with the Rokitansky-Kuster-Hauser syndrome and a leiomyoma of the right uterine fundus is presented. Eight years previously, she had undergone construction of an artificial vagina by the Counsellor modification of McIndoe's procedure. A review of the literature indicated that squamous cell carcinoma has occurred in the grafted skin and adenocarcinoma in the transplanted bowel segments used for the neovagina in these patients. Since many patients are lost to follow-up, the incidence of neoplasia may be greater than reported. (17 refs.)

- 78-2357 The Origins of Cervical Cancer: A Scanning Electron Microscopy Study.** (Eng) Murphy, J. M.



(Coombe Lying-in Hosp., Dublin, Ireland). *Ir J Med Sci* (10): 315-325; 1977.

necological surgery specimens from 247 women were examined by scanning electron microscopy to investigate the origin of cervical cancer. Based on examination of biopsy specimens, the first stages of squamous metaplasia were observed in the columnar villi, where the pattern of small cells was interrupted by larger ones with closely packed microvilli. With the progression of metaplasia, fusion of the columnar cells occurred and cuboidal cells developed in the superficial layers of the metaplastic epithelium. In the later stages of metaplasia, terminal bars formed between cells. Carcinoma in situ was characterized by a disorganized appearance of the epithelium at low magnification, and a granular appearance resulting from the numerous microvilli at high magnification. At high magnification, the surface structure of the dysplastic cells was intermediate between microridges and microvilli. Cytological specimens were classified as normal, intermediate, or abnormal according to the electron microscopic appearance, which was compared with that revealed by light microscopy (LM). Most cells that were normal on LM had normal surface features and those that appeared malignant had abnormal features. Dyskaryotic cells had a wide range of surface features that correlated with the degree of dyskaryosis at LM. These results indicate that scanning electron microscopy reveals changes in cell-surface characteristics that are not always apparent upon LM. (23 refs.)

78-2358 **Multiple Endocrine Neoplasia (M.E.N.) Type II--Case Report.** (Eng) Collins, M. P. Saint Vincent's Hosp., Dublin 4, Ireland; Hyland, M.; McMullin, J. P.; Muldowney, F. P. *Ir Med J* (18): 556-558; 1977.

This case report of a 43-yr-old woman with type II multiple endocrine neoplasia is presented. She had a pheochromocytoma of the right kidney, a left-sided medullary carcinoma of the thyroid, and a left lower pole parathyroid adenoma. This neoplasia has a genetic basis in an autosomal dominant gene; the etiological basis is probably centered in a genetic defect in the amine precursor uptake and decarboxylase cell system. (23 refs.)

78-2359 **Normotensive Familial Pheochromocytoma with Predominant Noradrenaline Secretion.** (Eng) Ho, A. D. (Medizinische Universitäts-Poliklinik, D-6800 Heidelberg, W. Germany); Feurle, G.; Gless, K.; Brandeis, W. E. *Br Med J* 1(6105): 81-82; 1978.

A 40-yr-old woman with familial pheochromocytoma was normotensive upon presentation despite a persistently raised urinary noradrenaline excretion. Her 8-yr-old son and one

of her sisters also had pheochromocytomas, but they were hypertensive. The absence of hypertension in this condition is unusual. (5 refs)

78-2360 **Cyanotic Heart Disease: "Low Altitude" Risk for Carotid Body Tumor?** (Eng) Nissenblatt, M. J. (Oncology Div., Johns Hopkins Hosp., Baltimore, MD, 21205). *John Hopkins Med J* 142(1): 18-21; 1978.

A 28-yr-old woman with cyanotic congenital heart disease developed a carotid body tumor. The lesion was resected without the occurrence of hypertension or arrhythmias. The tumor appeared to represent the response of the organ to the stresses of hypoxemia. Risk factors for carotid body tumors may include cyanotic heart disease in addition to the known risks of family history, prior papillary carcinoma of the thyroid, and high-altitude habitation. (26 refs)

See also:

\*(Rev.): 78-1805, 78-1812, 78-1815, 78-1816, 78-1817, 78-1819, 78-1820, 78-1821, 78-1822, 78-1823, 78-1824, 78-1825, 78-1830, 78-1842, 78-1844, 78-1856.

\*(Chem.): 78-1865, 78-1867, 78-1871, 78-1872, 78-1873, 78-1874, 78-1882, 78-1888, 78-1890, 78-1891, 78-1894, 78-1902, 78-1904, 78-1907, 78-1911, 78-1912, 78-1920, 78-1934, 78-1936, 78-1938, 78-1940, 78-1949, 78-1953, 78-1955, 78-1963, 78-1999, 78-2007, 78-2013, 78-2014, 78-2015, 78-2021, 78-2025, 78-2026, 78-2028, 78-2029, 78-2040, 78-2046, 78-2048, 78-2049, 78-2050, 78-2051, 78-2054, 78-2055, 78-2056, 78-2058, 78-2061, 78-2062, 78-2075, 78-2077, 78-2087, 78-2092, 78-2097, 78-2109, 78-2112, 78-2117, 78-2120, 78-2134, 78-2136, 78-2137, 78-2141, 78-2143, 78-2145, 78-2147, 78-2153, 78-2160, 78-2162.

\*(Phys.): 78-2167, 78-2168, 78-2171, 78-2178, 78-2181, 78-2182.

\*(Viral): 78-2206, 78-2233, 78-2237, 78-2241, 78-2245, 78-2268, 78-2276, 78-2304.

\*(Immun.): 78-2305, 78-2308, 78-2310, 78-2311, 78-2314, 78-2320.

\*(Epid.-Biom.): 78-2366, 78-2373, 78-2376, 78-2379.



- 78-2361 Preliminary Findings in a Mesothelioma Register (Meeting Abstract).** (Fre) Bignon, J. (Service de Pneumologie, Centre Hospitalier Intercommunal, 40, avenue de Verdun, 94010 Creteil, France); Di Menza, D.; Ruffie, P.; Bientz, M.; Nebut, M. *Rev Fr Mal Respir* 6(2): 213-214; 1978.

A history of definite or probable occupational exposure to asbestos was present in 75% of 550 registered cases of pleural mesothelioma. Since 1965, the number of cases has gradually increased. (no refs)

- 78-2362 Pleural Mesothelioma Register in Seine-Maritime, France.** (Fre) Lemerrier, J. P. (Service de Pneumologie, C.H.U. de Rouen, Hopital de Boisguillaume, 147, avenue du Marechal-Juin, 76230 Boisguillaume, France); Fondimare, A.; Tayot, J.; Desbordes, J.; Orange, N. *Rev Fr Mal Respir* 6(2): 209-211; 1978.

Exposure to asbestos was proved in 42/49 cases of pleural mesothelioma registered from reports by pathologists and pneumologists in the Seine-Maritime region of France. Duration of contact and latent period (1-45 yr) varied, and in all but three patients, exposure was occupational. (6 refs)

- 78-2363 Mesothelioma in the United States. Incidence in the 1970's.** (Eng) Hinds, M. W. (Occupational Health Section, Washington State Dept. Social and Health Services, Mail Stop LD-11, Olympia, WA, 98504). *J Occup Med* 20(7): 469-471; 1978.

Mesothelioma is a rare neoplasm, the occurrence of which has been clearly related to asbestos exposure. Data recently collected by population-based cancer registries in Washington, Hawaii, New Mexico, Connecticut, Michigan, Utah, Louisiana, and Iowa were obtained to determine mesothelioma incidence rates. These registries represent a total population of > 16 million persons. Crude incidence rates were found to range from 3.0 to 7.1/million/yr. Age-specific incidence rates showed a steady increase from the third through the eighth decade, and there was a more rapid increase for men than women. Sex-specific incidence rates, age adjusted to the 1970 US population, were found to range from 4.4 to 11.1/million/yr for men and from 1.2 to 3.8/million/yr for women. The highest rates for both men and women occurred in the New Orleans area of Louisiana and the Puget Sound area of Washington State, both with significant shipbuilding activity. (13 refs)

- 78-2364 Early Lung Disease in Asbestos-Product Workers.** (Eng) Mitchell, C. A. (Yale Univ. Lung Research Center, 105 LCI, 333 Cedar St., New Haven, CT, 06510); Charney, M.; Schoenberg, J. B. *Lung* 154(4): 261-272; 1978.

A total of 101 workers at a plant using asbestos to produce heat-resistant and friction composites underwent lung function tests to determine if any signs of lung disease were present. Chest auscultation results were 2+ in 25/79 exposed workers, compared with 1/22 nonexposed workers. Vital capacity was significantly reduced in 67% of the exposed workers. It is suggested that the exposed workers had signs of early parenchymal lung disease, even though radiologic examinations were within normal limits. (16 refs)

- 78-2365 Lung Cancer in Japanese Chromate Workers.** (Eng) Ohsaki, Y. (First Dept. Medicine, Faculty of Medicine, Hokkaido Univ., Sapporo, Japan); Abe, S.; Kimura, K.; Tsuneta, Y.; Mikami, H.; Murao, M. *Thorax* 33(3): 372-374; 1978.

Between 1972 and 1976, 10 cases of lung cancer occurred among workers in a Japanese chromate factory, and 4 additional cases were found through death certificates and medical records. All 14 patients were men (27-67 old), and all but 2 were heavy smokers. The period of exposure to chromate dust ranged from 10 to 36 yr (av 24.8 yr). Initial symptoms were hemoptysis in 3 patients, cough and expectoration in 6, wheezing in 1, and disturbance in gait in 1. Four patients had no specific complaints, and the cancer was found on routine examination. The histology in the 10 recent patients was squamous cell carcinoma in 7 and small cell anaplastic carcinoma in 3. The tumor occurred in the left lower lobe bronchus in 6 patients, the left upper lobe bronchus in 3, and the right lower lobe bronchus in 1. The incidence of lung cancer in chromate workers was calculated to be 657.9/100,000 compared with 13.3/100,000 for the entire Japanese population. (8 refs)

- 78-2366 The Role of Chronic Bronchitis in the Pathogenesis of Bronchogenic Lung Cancer.** (Pol) Pniewski, T. (Dept. Oddzial, Inst. Szpital Chorob Pluc, 91-520 Lodz, Poland); Wardowa, A. *Pol Tyg Lek* 33(1): 591-593; 1978.

Bronchogenic lung cancer was diagnosed in 50/289 patients with chronic bronchitis treated at a hospital during 1975-1976. The incidence (17.3%) was increased significantly.



y compared with that in the general population. The cancer occurred in 4/35 patients aged <40 yr, 38/134 aged 40-60, and 8/120 aged >60. The findings indicate that chronic bronchitis patients 40-60 yr old have a high risk of developing bronchogenic cancer, which justifies more frequent cytological examinations in this age group for early diagnosis of this cancer. (14 refs)

- 8-2367 **Changes in Mortality due to Bronchogenic Cancer and All Cancers in Switzerland, 1970-1975. Concurrent Changes in Tobacco Consumption.** (Fre) Cardis, E. (Av. des Mousquines 38, 1005 Lausanne, Switzerland). *Cancer Inf (Bern)* 12(4): 138-145; 1977.

Changes in the incidence and mortality rates of bronchogenic cancer in Switzerland from 1970 to 1975 are reviewed. The mortality rate for both sexes increased, but in 1975 it was still greater for men. The number of deaths from bronchogenic cancer represented a smaller proportion of the total cancer deaths for men in 1975 than in 1970, but the opposite was true for women. The incidence of bronchogenic cancer appears to be increasing in women and decreasing in men. Mortality due to all cancers is also increasing in women and decreasing in men, a fact that may be related to the trends in bronchogenic cancer. The tobacco industry, in terms of production, importation, and exportation of cigarettes, peaked in 1972 and has since declined except for a slight rise in 1975. Although the statistics are not precise, there is evidence of a decline in daily consumption of cigarettes from 30/day in 1972 to 20/day in 1975 in smokers >20 yr of age. About two-thirds of the male population and one-third of the female population were smokers in both years. (3 refs)

- 8-2368 **Incidence of Cancer of the Oral Cavity and Pharynx, Particularly in Men, in the Cantons of Neuchâtel and Geneva (Meeting Abstract).** (Fre) Obradovic, M. (Registre genevois des tumeurs, Geneva, Switzerland); Roch, R. *Cancer Inf (Bern)* 12(3): 101; 1977. (no refs)

- 8-2369 **Etiology and Epidemiology of Carcinomas of the Mouth and Pharynx (Meeting Abstract).** (Fre) Pasche, R. (Clinique universitaire d'oto-rhino-laryngologie, CHUV, Lausanne, Switzerland); Junod, B. *Cancer Inf (Bern)* 12(3): 89; 1977. (no refs)

- 8-2370 **Epidemiological Evaluation of Sunlight as a Risk Factor of Lip Cancer.** (Eng) Lindqvist, C.

(Finnish Cancer Registry, Liisankatu 21B, 00170 Helsinki 17, Finland); Teppo, L. *Br J Cancer* 37(6): 983-989; 1978.

A total of 3,169 cases of lip cancer in men and 303 cases in women were diagnosed in Finland and reported to the Finnish Cancer Registry during 1953-1973. The diagnosis was verified histologically in 95% of the cases in men and in 92% in women. The mean annual age-adjusted incidence rate was 7.3/10<sup>5</sup> in men and 0.5/10<sup>5</sup> in women. The annual incidence for men has decreased since the early 1960's. The decrease involved all age groups and was not due to a cohort effect. Only a very slight decrease in risk was observable in women. The incidence was clearly higher in rural than in urban areas, the urban/rural ratio of the age-adjusted incidence rates being 0.6 for men. A decrease in risk with time was observable for both urban and rural populations. The risk was highest in the northern and eastern parts of the country, for both urban and rural areas. It was concluded that the decrease in the incidence of lip cancer in Finland cannot be accounted for solely by urbanization. An inverse relationship was found between the mean annual amount of solar radiation and the risk of lip cancer. The results are not in accordance with the theory of the association between exposure to actinic radiation and the risk of lip cancer. The synergistic action of other factors related to outdoor occupation and, probably, smoking would provide a better explanation for these observations. (26 refs)

- 78-2371 **Increase in Malignant Melanoma Incidence Following Sunspot Cycles (Meeting Abstract).** (Eng) Houghton, A. (Dept. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT); Viola, M. V. *Clin Res* 26(3): 486A; 1978. (no refs)

- 78-2372 **Melanoma in Connecticut.** (Eng) Viola, M. V. (Oncology Div., Univ. Connecticut Health Center, Farmington, CT, 06032); Houghton, A. *Conn Med* 42(4): 268-269; 1978.

An alarming increase in skin melanoma in Connecticut is reported. Incidence rates are highest in towns along the coast and in affluent white suburbs. It is suggested that exposure to solar radiation (UV light flux is 10%-20% higher along the coast) and recreational habits (duration and intensity of sun exposure and type of clothing), as well as factors that affect UV light flux at the earth's surface, are responsible for the increased incidence of the disease. (8 refs)

- 78-2373 **Relationship Between Arsenic Intake and Internal Malignant Neoplasms.** (Eng) Reymann, F. (Dept. Dermatology, Finsen Inst., 49 Strandboulevard,



DK-2100 Copenhagen, Denmark); Moller, R.; Nielsen, A. *Arch Dermatol* 114(3): 378-381; 1978.

The relationship between arsenic intake and internal malignant tumors was studied in 53 Danish patients with arsenic keratoses and 389 patients who were treated with arsenic for various skin diseases in the 1930's. Based on figures from the Danish Cancer Registry, the incidence of internal cancer was not increased in the arsenic-treated group as a whole. The incidence was, however, significantly increased among women who had been treated for multiple basal cell carcinoma (5 cases observed vs 1.2 expected), and it was significantly decreased in women who had been treated for lichen planus (6 vs 15.3). A nonsignificantly decreased incidence of internal cancer was also observed in women who had had lichen planus but had not been treated with arsenic. Deaths from internal cancer occurred at almost twice the expected rate among the arsenic keratoses patients, although no regular statistical analysis could be made on this specifically selected group. The incidence of both arsenic keratoses and internal malignant neoplasms seems to increase with the amount of arsenic taken. The data suggest that arsenic has a carcinogenic effect even in relatively small doses and that it should not be used in human therapy. (14 refs)

**78-2374 Gastric Cancer in a Coal Mining Region.** (Eng) Klauber, M. R. (Dept. Family and Community Medicine, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132); Lyon, J. L. *Cancer* 41(6): 2355-2358; 1978.

The incidence of gastric cancer in the coal mining counties of Utah (Carbon and Emery) was studied based on all new gastric cancer patients reported to the Utah Tumor Registry during 1970-1975. Age-adjusted rates of gastric cancer for Carbon and Emery Counties and all of Utah during this period were 6.9, 8.2, and 6.3, respectively. The standardized incidence ratios (SIR) for the two counties were 110 and 129, respectively. The differences between the adjusted rates for Carbon and Emery County combined and the rest of the state were not significant for either sex or both sexes combined. The incidence of gastric cancer in the two counties did not vary significantly by year during 1966-1975; for both counties, there was an excess incidence during 1965. The significant difference in SIR for the periods 1965-1969 and 1970-1975 was due largely to the increased incidence during 1965. A likely explanation for this excess is that it was the result of chance clustering. The previous suggestion that the high incidence of gastric cancer in Carbon and Emery Counties during 1965-1969 could be related to frequent exposure to coal-carrying hydrocarbons appears unwarranted. (6 refs)

**78-2375 High Gastric Cancer Incidence in San Marino: Familial Factors (Meeting Abstract).** (Eng) Jackson, C. E. (Henry Ford Hosp., Detroit, MI); Brownlee,

R. W.; Schuman, B. M.; Micheloni, F.; Ghironzi, G. *Gastroenterology* 74(5, part 2): 1048; 1978. (no refs)

**78-2376 Pancreatic Cancer. Etiological and Clinical Observations of 140 Cases.** (Ita) Gullo, L. (Osedale S. Orsola, Bologna, Italy); Ventrucci, M.; Costa, P. L.; Procaccio, L.; Nestico, V.; Ripani, R. *Recent Prog Med (Roma)* 64(1): 90-97; 1978.

Epidemiological and clinical observations of 140 patients with cancer of the pancreas are presented. The 140 cases were diagnosed among 3,455 patients with digestive tract tumors admitted to hospitals in Bologna, Italy, during 1962-1972. The patients included 99 men and 41 women age 21- > 80 yr with a median age of 57.9 yr for men and 62.2 yr for women. Compared with 8,329 healthy blood donors, the frequency of blood group A was significantly higher among the patients with cancer of the pancreas (55.6% vs 43.8%). Eight of these patients had a history of diabetes, two chronic pancreatitis. The first symptoms were anorexia and dyspepsia in 87 patients, jaundice in 50, pain in 91, emesis in 22, pruritus in 21, fever in 15, loss of wt in 60. The objective signs included hepatomegaly in 87 patients, splenomegaly in 7, Courvoisier-Terrier sign in 22, epigastric mass in 29, and ascites in 20. (21 refs)

**78-2377 Geographic Correlates of Pancreas Cancer in the United States.** (Eng) Blot, W. J. (Environmental Epidemiology Branch, NCI, Bethesda, MD, 20014); Fraumeni, J. F.; Stone, B. J. *Cancer* 42(1): 373-380; 1978.

Age-adjusted death rates for pancreas cancer during 1950-1969 were correlated by sex and race with demographic and industrial data for the 3,056 counties of the contiguous US. Only a small fraction of the county-to-county variation in mortality was explained by these variables, in contrast to their strong correlation with other common neoplasms. The only geographic cluster occurred in an area encompassing parts of Louisiana and Mississippi. Throughout the country, however, the rates for pancreas cancer were higher in urban areas, especially in men, and in counties with many residents of Scandinavian and East European (particularly Russian) descent. No associations were found with socioeconomic, industrial, or alcohol-consumption indices. The mortality patterns for pancreas and lung cancers were highly correlated in men, suggesting the influence of tobacco consumption on both tumors. In women, pancreas cancer was significantly correlated with diabetes mellitus, consistent with other evidence linking these two diseases. (23 refs)

**78-2378 Cancer of the Bladder in Southern Iran.** (Eng) Sadeghi, A. (Dept. Radiation Therapy, Ne



e Hosp., Shiraz, Iran); Behmard, S. *Cancer* 42(1): 156; 1978.

sex ratio for cancer of the bladder among male and hospitalized patients in Southern Iran is estimated to out 9:1. Differential case ascertainment may account some of the discrepancy. However, when the same data was used, no other major cancer site was found to have ratio of this nature. Since industrial carcinogens and predisposing factors such as schistosomiasis are rare, role of other etiologic factors such as opium addiction, which predominates in men, are considered and discussed. (5 refs)

2379 **Incidence of Primary Liver Cancer in Necropsies Performed in Vitoria, Brazil.** (Por) Pereira, (Disc. de Patol. do Dep. de Biol., Univ. Fed. do Espirito Santo, Vitoria, Espirito Santo, Brazil); Boni, E. S.; Filho, A. Filho, J. L.; Goncalves, C. S. *Rev Assoc Med Bras* 23(12): 422; 1977.

ten cases of primary liver carcinoma were found among cases of malignant tumors in a series of 807 autopsies performed in 1966-1968 in the hospitals of Vitoria, State of Espirito Santo, Brazil. All patients were aged 17-74 yr, 11 of which were aged  $\geq 42$  yr. There were 11 men and 5 women. Liver carcinoma was found in 4 cases, multinodular carcinoma in 11, and diffuse carcinoma in 1. Three solid carcinomas were in the right lobe, one in the left; four multinodular carcinomas were in the right lobe, one in the left. Lobes were involved in the seven other cases. Metastases were found in 13 patients; they included 7 pulmonary metastases and 10 lymph node metastases. The findings indicate high frequency of primary liver carcinoma in the State of Espirito Santo compared with other regions of Brazil. (17 refs)

2380 **Familial History and Risk of Breast Cancer (Meeting Abstract).** (Eng) Speizer, F. E. (Channing Lab., Dept. Medicine, Harvard Medical Sch., Boston, MA); Hennekens, C. H.; Rosner, B.; Bain, C.; Belanger, C. *Res* 26(3): 282A; 1978. (no refs)

2381 **Epidemiology of Mammary Fibroadenoma (Meeting Abstract).** (Spa) Ruiz-Moreno, J. A. (Hospital Central Militar, Mexico City, Mexico); Medina-Malagon, L. E.; Rosales-Perez, P. *Patologia (Madr)* 195; 1977. (no refs)

2382 **Comparison of Age-specific Mortality from Breast Cancer in Males in the United States and**

**Japan.** (Eng) Moolgavkar, S. H. (Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111); Lee, J. A.; Hade, R. D. *J Natl Cancer Inst* 60(6): 1223-1225; 1978.

Mortality data on male breast cancer in the US and Japan were analyzed. The logarithm of the mortality rate increased linearly with the logarithm of age, and it had a slope of about 5. Mortality in Japan was about one-fourth that in the US, but the relationship to age was similar. Thus, the age-specific mortality curves of male breast cancer mimic those of many epithelial tumors and do not exhibit the peculiarities of the curves for female breast cancer. (37 refs)

78-2383 **The Epidemiology of Breast Cancer in 785 United States Caucasian Women.** (Eng) Wynder, E. L. (Div. Epidemiology, American Health Foundation, 320 E. 43rd Street, New York, NY, 10017); MacCornack, F. A.; Stellman, S. D. *Cancer* 41(6): 2341-2354; 1978.

A retrospective case-control hospital study of 785 Caucasian breast cancer patients and 2,231 age-stratified controls was conducted in New York City from 1969-1975. Demographically, the case and control groups were similar, and there were no significant differences in age at menarche, height/weight, use of conjugated estrogens or oral contraceptives, or surgical history. Long menstrual periods were more common among the patients, but the relative risk estimate was greater only among postmenopausal women. Late menopause was more common among the patients and early menopause was more common among the controls. Late age at first birth (AFB) was a significant risk factor for pre- and perimenopausal women; however, nulliparous women were at greater risk for breast cancer than women with early AFB in all three menopausal groups. Age at last birth was not a risk indicator. Moderate and severe premenstrual symptoms were associated with significantly greater risk among pre- and perimenopausal women, and premenopausal symptoms of chills, hot flashes, and changes in cycle and flow were associated with greater risk in peri- and postmenopausal women. Benign breast disease was nonsignificantly associated with higher risk in all menopausal groups, but pre- and perimenopausal women who had a mother with a history of breast cancer had a higher risk for the disease. Risk variables determined by this and other case-control studies cannot account for the magnitude of differences in the international incidences of breast cancer. (63 refs)

78-2384 **Recent Trends in the Incidence and Mortality of Cancer of the Uterine Corpus in Connecticut.** (Eng) Marrett, L. D. (Connecticut Cancer Epidemiology Unit, Yale Univ., 30 College St., New Haven, CT, 06510); Elwood, J. M.; Meigs, J. W.; Flannery, J. T. *Gynecol Oncol* 6(2): 183-195; 1978.

The incidence of cancer of the uterine corpus in Connecticut



during 1960-1975 was determined according to age, stage of disease, and time of diagnosis: mortality from this tumor was determined according to age and year of death. Case material was obtained from the Connecticut Tumor Registry. The age-adjusted rates for each stage of uterine cancer were comparable during 1960-1964 and 1965-1969, but the age-adjusted rate for invasive disease was nearly 20% higher during 1970-1975 than in either of the two earlier periods. This excess reflects a higher rate of localized corpus cancer, as the incidence of tumors with regional or distant spread was unchanged. Women aged 50-59 yr experienced the largest increase in localized disease in the later time period, although the rate was increased in all women > 50 yr. The age-adjusted rates of localized disease increased consistently during each 2-yr period since 1970, this increase being observed in every age group over 50 yr except the 70 to 90 yr group. The rate of regional or distant disease in the 50 to 59 yr group was also higher in each 2-yr period since 1970. Diagnoses of carcinoma in situ of the endometrium increased from an av of 13.2 cases/yr in 1960-1964 to 20.6 cases/yr in 1965-1969 and to 32.7 cases/yr in 1970-1975. Mortality rates from cancer of the uterine corpus have declined slightly over the 15-yr period. The recent increase in the incidence of localized invasive endometrial cancer in women  $\geq 50$  yr is probably at least partially due to the increasing use of estrogen therapy, although hysterectomy rates and diagnostic practices and criteria are also important influences. (52 refs)

**78-2385 Contacts Among Patients with Hematological Malignancies.** (Eng) Gunz, F. W. (Dept. Medical Res., Kanematsu Memorial Inst., Sydney Hosp., Sydney, N.S.W. 2000, Australia); Gunz, J. P.; Leigh, J. *Cancer* 41(6): 2379-2387; 1978.

A survey was carried out in two country areas of New South Wales, Australia, to define contacts among 184 patients with lymphoma, leukemia, and myeloma and to determine whether these were more numerous among the patients than among matched controls from the same local hospital populations. Thirty-nine of the 184 patients could not be included for various reasons, and therefore 145 were interviewed along with the same number of controls. The overall distribution of cases was not significantly different from that expected based on the incidence for all of New South Wales in 1972, although there was a significant deficit in Hodgkin's disease and a significant excess of all leukemias in Area 1. Of the 290 cases and controls, 111 had one or more contacts with other patients or controls (37.9% of patients and 38.6% of controls). There were 24 patient-patient contacts involving 33 individual patients, 23 control-control pairs involving 36 individuals, and 38 patient control contacts involving 66 individuals. A statistical analysis using a weighting system showed that numbers, closeness, and duration of contacts among patients and patients did not differ significantly from those expected. The results do not support the thesis that leukemia and lymphoma are transmitted by infectious agents. (18 refs)

**78-2386 The Use of Retirees to Evaluate Occupational Hazards. II. Comparison of Cause Specific Mortality by Work Area.** (Eng) Collins, J. F. (Cooperative Studies Program Coordinating Center, Veterans Admin Hosp., Perry Point, MD); Redmond, C. K. *J Occup Med* 20(4): 260-266; 1978.

The usefulness and limitations of retiree mortality studies for occupational mortality studies, rather than a total workers cohort, are evaluated in the blast furnace, janitorial, and coke plant divisions of seven steel plants. The retiree studies detected occupational hazards such as respiratory cancers and nonmalignant respiratory disease, but the estimated average relative risk tended to be greater than that for the total cohort of workers. Problems with the use of retirees included the small sample sizes, the retiree study not indicating significant excess deaths from certain diseases because excess mortality had taken place at younger ages, and differences between the estimates of risk for the retiree study and the total cohort study. The estimates of risk for the study using all men > 65 yr did not vary from the estimates of risk for the total cohort as much as the risks from the retirees did. However, the exclusion of nonretirees from the retiree study did not appear to affect the overall conclusions. It is concluded that retiree studies may be useful tools in detecting occupational hazards, but spurious negative findings may result from the limited age group being studied and the small sample size. (19 refs)

**78-2387 Mortality Follow-up of Workers Exposed to 1,4-Dioxane.** (Eng) Buffler, P. A. (Dept. Preventive Medicine and Community Health, 140 Kedler Building, Univ. Texas Medical Branch, Galveston, TX, 77550); Wood, S. M.; Suarez, L.; Kilian, D. J. *J Occup Med* 20(4): 255-259; 1978.

The carcinogenic effect of 1,4-dioxane was studied in 100 workers in the manufacturing area and 65 workers in the processing area of a dioxane manufacturing plant. The workers had been employed between April 1954 and June 1975 and had served at least 1 mo in the given areas; the exposure in the areas was determined to be < 25 ppb. There were seven deaths among the manufacturing area workers and five among the processing area workers. Of the former, one died of carcinoma of the stomach (28 mo exposure) and one of alveolar cell carcinoma (38 mo exposure); of the latter, one died of a malignant mediastinal tumor with generalized metastases (12 mo exposure). This total of three deaths from malignant tumor was not significantly greater than the 1 expected. A comparison of workers with intermittent exposure and those with continuous exposure revealed nearly identical incidences of mortality. The seven deceased persons in the manufacturing area also had exposure to other chemicals, and the five in the processing area were also exposed to vinyl chloride. These observations were based on small



Numbers of deaths of employees who were apparently exposed at low levels and for relatively short exposures. (12 refs)

78-2388 **Cancer Incidence in a Religious Isolate of Alberta, Canada, 1953-74.** (Eng) Gaudette, L. A. Dept. Biostatistics, Analysis and Cancer Registry, Provincial Cancer Hosps. Board, Edmonton, Alberta, Canada T6G 2Z2; Holmes, T. M.; Laing, L. M.; Morgan, K.; Grace, M. *J Natl Cancer Inst* 60(6): 1233-1238; 1978.

Cancer incidence was studied among the 6,700 Hutterites who live in 82 colonies in the province of Alberta, Canada, and who comprise >30% of the Hutterite population of North America. This Christian sect is a genetic isolate with distinctive life style of communal living and diversified farming. The numbers of their cancer cases ascertained from 1953 to 1974 were compared with those expected from Alberta Cancer Registry rates. The overall incidence of registered cancer cases among Hutterite women was significantly less than expected (48 observed, 74.2 expected), but in the men the overall incidence did not differ from that expected (52 observed, 56.5 expected). There were significantly fewer cases than expected of lung cancer in men and of carcinoma in situ of the cervix uteri in women. A significantly higher incidence of stomach cancer was found in the sect's men. Data on a family with two cases of stomach cancer contributed to this observed excess of stomach cancer. (33 refs)

78-2389 **Malignant Tumors in Some Ethnic Groups of Kazakh SSR.** (Rus) Kairakbaev, M. K. (Lab. Tumor Epidemiology, Kazakh Res. Inst. Oncology and Radiology, Alma-Ata, USSR). *Vopr Onkol* 24(6): 100-104; 1978.

The incidence of malignant tumors among the various ethnic groups of Kazakh SSR (USSR) is reviewed. The morbidity index (per 100,000) for cancer of the esophagus was significantly greater among the Kazakhs (59.0 in men and 60.6 in women) than among Russians (8.3 and 5.6, respectively). Breast, cervical, and ovarian carcinoma morbidity among Kazakh women was lower than that among Russian women. (18 refs)

See also:

\*(Rev.): 78-1810, 78-1816, 78-1817, 78-1819, 78-1827, 78-1829, 78-1833, 78-1834, 78-1835, 78-1836, 78-1837, 78-1839, 78-1847, 78-1848, 78-1854, 78-1857, 78-1858, 78-1859.

\*(Chem.): 78-1867, 78-1873, 78-1903, 78-1929, 78-1930, 78-2001, 78-2020, 78-2036, 78-2046, 78-2051, 78-2082, 78-2094, 78-2102, 78-2119, 78-2133, 78-2148, 78-2158, 78-2159.

\*(Phys.): 78-2179, 78-2192.

\*(Path.): 78-2348, 78-2350.



## MISCELLANEOUS

- 78-2390 Squamous Metaplasia of the Tracheal Epithelium in Organ Culture. II. Nutritional Influences.** (Eng) Mossman, B. T. (Dept. Pathology, Univ. Vermont Coll. Medicine, Burlington, VT, 05401); Heintz, N.; MacPherson, B. V.; Craighead, J. E. *Proc Soc Exp Biol Med* 157(3): 500-505; 1978.

The nutritional constituents present in Waymouth's medium, which supports squamous metaplasia of hamster tracheal mucociliary epithelium, but absent from Eagle's minimum essential medium (MEM), which does not support this metaplasia, were examined. These nutritional constituents were divided into five groups: (1) insulin and glutathione; (2) vitamins C, B<sub>12</sub>, and biotin; (3) nucleic acid intermediate (4) inorganic salts; and (5) nonessential amino acids. The nonessential amino acids were important in enhancing metaplasia and keratinization when mucociliary epithelium was cultured in MEM. Individual addition of the nonessential amino acids to MEM indicated that L-glutamic acid and L-serine seemed to be the most influential in inducing metaplastic changes. (32 refs)

- 78-2391 Aminophospholipid Asymmetry in a Tumorigenic Murine Fibroblast Grown with Choline Analogues in the Absence of Serum (Meeting Abstract).** (Eng) Fontaine, R. N. (Dept. Pharmacology, Univ. Missouri Sch. Medicine, Columbia, MO, 65201); Schroeder, F. *Fed Proc* 37(6): 1597; 1978. (no refs)

- 78-2392 A Protease-resistant, Transformation-sensitive Membrane Glycoprotein and an Intermediate Filament-forming Protein of Hamster Embryo Fibroblasts.** (Eng) Carter, W. G. (Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104); Hakomori, S. *I. J Biol Chem* 253(8): 2867-2874; 1978.

A transformation-sensitive membrane glycoprotein with a subunit mol wt of 170,000 (170K) and an intermediate filament-forming protein (IFP) with a mol wt of 56,000 (56K) were purified from Syrian hamster embryo fibroblasts, and the possible interaction of these components was investigated. The 170K glycoprotein was characterized as follows: (1) weak surface labeling by either lactoperoxidase-catalyzed iodination or galactose oxidase oxidation and reduction with (<sup>3</sup>H)-labeled sodium borohydride; (2) strong metabolic labeling with (<sup>3</sup>H)glucosamine; (3) resistance to trypsin digestion; (4) deletion in clones of polyoma-transformed NIL cells; and (5) possession of a disulfide-dependent subunit interaction. The 56K IFP had an electrophoretic mobility distinct from

either actin or tubulin, and it could be polymerized in the presence of millimolar quantities of guanosine triphosphate and magnesium and calcium ions at 25 C to form filament of 105 Å diameter. The polymerization of IFP was increased by calcium ion and inhibited by addition of reduced glutathione or dithiothreitol to the sucrose/ATP extraction buffer. IFP could be copurified with 170K glycoprotein from the cold sucrose/ATP extract of cells through a *Ricinus communis* lectin-polyacrylhydrazido-Sepharose column, although IFP has no receptor for *R. communis* lectin. IFP and 170K glycoprotein were coprecipitated when IFP was polymerized from sucrose/ATP extracts of cells. These findings suggest a possible interaction between the IFP and 170K glycoprotein. (43 refs)

- 78-2393 Cell Surface Glycoproteins in Cellular Adhesion, Membrane Transport, and Malignant Transformation (Meeting Abstract).** (Eng) Yamada, K. M. (NIH, Bethesda, MD, 20014); Pastan, I.; Pratt, R. M.; Olden, K. *In Vitro* 14(4): 353-354; 1978. (no refs)

- 78-2394 Alteration of Cell Surface-Proteins in Proliferative and Neoplastic Lesions of Human Epidermis Demonstrated with Indirect-Immunofluorescence (Meeting Abstract).** (Eng) Bolling, R. (Universitäts-Hautklinik, Göttingen, Göttingen, W. Germany); Mahrle, G. *Arch Dermatol Res* 261(1): 92; 1978. (no refs)

- 78-2395 Structural Studies on the Heparan Sulfates Produced by Parent and Transformed Swiss Mouse 3T3 Cells (Meeting Abstract).** (Eng) Keller, J. M. (Univ. Health Sciences/Chicago Medical Sch., Chicago, IL, 60612); Keller, K. L.; Johnston, L. S. *Fed Proc* 37(6): 1729; 1978. (1 ref)

- 78-2396 Structural Alterations in Heparan Sulphate after Selection of Highly Tumorigenic Cells from Two Independent Mouse Clones (Meeting Abstract).** (Eng) Winterbourne, D. J. (NIH, NCI, Bethesda, MD, 20014). *Fed Proc* 37(6): 1729; 1978. (no refs)

- 78-2397 Prolactin Receptors in Mammary Tumors of GR Mice.** (Eng) Costlow, M. E. (Dept. Bio



mistry, St. Jude Children's Res. Hosp., Memphis, TN, 38101); Sluyser, M.; Gallagher, P. E. *Endocr Res Commun* 2: 285-294; 1978.

presence of prolactin receptors in murine mammary tumors was studied in ovariectomized GR mice in whom tumors were induced by 3-4 mo continuous treatment with estrone and progesterone.  $^{125}$ I-labeled ovine prolactin binding to homogenates of these tumors reached a steady state within 1 hr at 22°C and remained essentially constant for 24 hr. Nonspecific binding accounted for about 38% of the total binding. The steady-state prolactin binding was highest in primary tumors, being reduced to 62%, 30%, and 5% of this level in transplanted hormone-dependent tumors, transplanted hormone-responsive tumors, and transplanted autologous tumors, respectively. The reductions in prolactin binding were due to a reduction in the number of receptor sites. The number of receptor sites in the primary tumors was comparable to that in liver from a normal female mouse. The data indicate that prolactin receptors are a useful marker for hormone dependence in mammary tumors of GR mice. The loss of prolactin may be a key step in the transition to autonomy. Autonomous growth may result from an increase in the relative proportion of autonomous cells present in the tumor. (4 refs.)

**2398 Removal of 5-Bromo-2-deoxyuridine Incorporated in Liver DNA of Newborn and Young Adult Rats.** (Eng) Arfellini, G. (Inst. Cancerology, Univ. Bologna, via S. Giacomo 14, 40126 Bologna, Italy); Prodi, G.; Bazzani, S. *Experientia* 34(2): 185-186; 1978.

Removal of  $^{14}$ C-5-bromo-2-deoxyuridine (BUdR) from DNA in newborn and female young adult Wistar rat liver was investigated. All rats were inoculated with a mixture of  $^3$ H-BUdR and  $^3$ H-thymidine, and the time course of the removal was followed using a  $^3$ H/ $^{14}$ C ratio. The results in the DNA of newborns and adults 1 hr after injection were quite different (3.86 and 13.19, respectively). They also differed from the ratio of the injected mixture (7.0) and from the ratio found in regenerating rat liver (7.04). These differences in nucleotide uptake could be due either to a dilution of the labeled compounds in the different cell nucleotide pools or to a lower discriminating capacity of DNA polymerases of newborns as regards BUdR incorporation. A significant BUdR removal from liver DNA began 2 days after treatment in adults, but only after 21 days in newborns. The amount of BUdR removed was threefold in newborns but less than twofold in adults, even considering the ratio between the last and first determinations; this could be due to incorporation of excised BUdR into growing livers. (8 refs.)

**2399 Deoxyribonucleic Acid Structure in Human Diploid Fibroblasts Stimulated to Proliferate.** (Eng) Collins, J. M. (Medical Coll. Virginia/Virginia Commonwealth Univ. Cancer Center, Health Sciences Div., Virginia Commonwealth Univ., Richmond, VA 23298). *J Biol Chem* 252(1): 141-147; 1977.

When contact-inhibited human diploid fibroblasts that have been maintained on medium containing 0.5% serum were stimulated by 10% serum, they left the  $G_0$  state and entered the cell cycle at  $G_1$ . The onset of DNA synthesis occurred at 12-13 hr. DNA isolated from cultures that had been stimulated for up to 30 hr was characterized in terms of sensitivity to a single-strand-specific nuclease,  $CsSO_4/AgClO_4$ , buoyant density, sedimentation in neutral and alkaline sucrose gradients, and sedimentation in neutral sucrose gradients after digestion with  $S_1$  nuclease. The amount of single-strandedness increased after 4 hr as indicated by sensitivity to  $S_1$ -nuclease and buoyant density. The amount of single-strandedness increased as the cells entered the S phase and decreased as they entered  $G_2$ . The DNA isolated from  $G_0$  cells behaved as native, duplex DNA with virtually no breaks. The DNA from 2- and 4-hr-stimulated cultures contained a significant number of breaks. The number of breaks reached a max in the S phase and declined as the cells entered  $G_2$ . There were no nuclease-sensitive sites (gaps) in  $G_0$  or 2-hr cultures. The number of sites increased 4 hr after stimulation, reached a max during the S phase, and decreased as the cells entered  $G_2$ . These results suggest a chromosomal cycle at the level of DNA itself, whereby structural changes occurring throughout the  $G_1$  are aimed at the initiation of DNA synthesis. These changes reach a max during replication and decline as replication is terminated. (42 refs.)

**78-2400 Enzymatic Synthesis of DNA Complementary to Mitochondrial mRNA via Reverse Transcription.** (Eng) Frolova, L. (Inst. Molecular Biology, USSR Acad. Science, Vavilov Str. 32, Moscow 117312, USSR); Arsenyan, S.; Avdonina, T.; Gaitskhoki, V.; Kisselev, O.; Neifach, S.; Kisselev, L. *Nucleic Acids Res* 5(1): 285-295; 1978.

An attempt was made to synthesize complementary DNA by reverse transcription using the polyadenosine [poly(A)]-containing mitochondrial messenger RNA's (mRNA's) of rat liver, oligo(dT) primer, and the RNA-directed DNA polymerase from avian myeloblastosis virus. Mitochondrial mRNA did not support DNA synthesis under the standard conditions sufficient for the reverse transcription of rabbit globin mRNA and poly(A) in the presence of the oligo(dT) primer. After mild alkaline treatment of the mRNA and subsequent polyadenylation of the 3' termini of the generated fragments with the ATP:RNA adenylyltransferase from *Escherichia coli*, the poly(A)-positive polyribonucleotides were able to serve as templates for reverse transcription. It is concluded that a structural block exists in mitochondrial mRNA nontranslatable regions adjacent to the poly(A) terminal sequence. This block could be caused by posttranscriptional modification of the mRNA or by a stable secondary structure in this mRNA region. (17 refs.)



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1. The first part of the document is a list of names and their corresponding dates. The names are: John Doe, Jane Smith, and Bob Johnson. The dates are: 1990, 1991, and 1992.







